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Review Article

A SCIENTIFIC UPDATE ON NANOTECHNOLOGY: A REVIEW

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ABSTRACT

The use of nanotechnology in medicine has the potential to have a major impact on human health for the prevention, diagnosis, and treatment of diseases. One particular aspect of the nanomedicine field which has received a great deal of attention is the design and development of nanoparticulate nanomedicines (NNMs) for drug delivery (i.e., drug-containing nanoparticles). NNMs are intended to deliver drugs via various mechanisms: solubilization, passive targeting, active targeting, and triggered release. The NNM approach aims to increase therapeutic efficacy, decrease the therapeutically effective dose, and/or reduce the risk of systemic side effects. In order to move a NNM from the bench to the bedside, several experimental challenges

need to be addressed. This review will discuss the current trends and challenges in the clinical translation of NNMs as well as the potential pathways for translational development and commercialization. Key issues related to the clinical development of NNMs will be covered, including biological challenges, as biomarkers, ability to locate and treat tumours, delivering the genetic material etc., comparison to current therapies.

KEYWORDS: Nanomedicine, Nanoparticles, Drug delivery systems, Biomarket, Osteoarthritis.

INTRODUCTION

Nanomedicine applies nanotechnology to highly specific medical interventions for the prevention, diagnosis, and treatment of diseases (Teli et al., 2010). In the last several decades, the application of nanotechnology for medical purposes has received significant attention from researchers, academia, funding agencies, government, and regulatory bodies (Allen and Cullis, 2004; Sercombe et al., 2015; Hare et al., 2017). One particular aspect of the

nanomedicine field which has received a great deal of attention is the design and development of nanoparticulate nanomedicines (NNMs) for drug delivery (i.e., drugcontaining nanoparticles), which are most often given by parenteral (particularly intravenous) administration. NNMs are intended to increase the therapeutic index of drugs (i.e., increase efficacy and/or reduce toxicity) by delivering them via various mechanisms: solubilization, passive targeting, active targeting, and triggered release (Figure (Figure 1).1). Nanoencapsulation gives the opportunity to protect fragile compounds that degrade easily in biological environments and to provide solubilization, i.e., to deliver compounds which have physicochemical properties that strongly limit their aqueous solubility and therefore systemic bioavailability (Talekar et al., 2015; Kim et al., 2016; Larsson et al., 2017; Mishra et al., 2017; Shajari et al., 2017). Targeted drug delivery and triggered release of NNMs have been shown to be beneficial for increasing the therapeutic index of compounds, by improving the in vivo fate of drug molecules such that more efficient delivery to the target site is achieved (to yield improved therapeutic effects) with less accumulation in many healthy body sites (to reduce toxicity). Also NNMs have been studied for their ability to stimulate target cell uptake and improve intracellular trafficking, processes sometimes required when they have localized in target tissues (Mastrobattista et al., 1999; Hua, 2013; Hua et al., 2015).

Although NNMs have demonstrated significant therapeutic advantages for a multitude of biomedical applications, their clinical translation has not progressed as rapidly as the plethora of positive preclinical results would have suggested (Luxenhofer et al., 2014). In order to move a NNM from the bench to the bedside, several experimental challenges need to be addressed. From a biological perspective, these include studies focused on understanding the in vivo fate and interactions of NNMs with the blood, tissue, cellular, and intracellular compartments in the host in healthy and diseased states (Nehoff et al., 2014; Sercombe et al., 2015; Hare et al., 2017). For NNMs to have clinical translation potential, the complexity in their design and development also needs to be minimized as much as possible to create systems that are able to be reproducibly prepared and characterized (Lammers, 2013; Barz et al., 2015). This review will address the current trends and challenges in the clinical translation of NNMs as well as the potential pathways for translational development and commercialization.

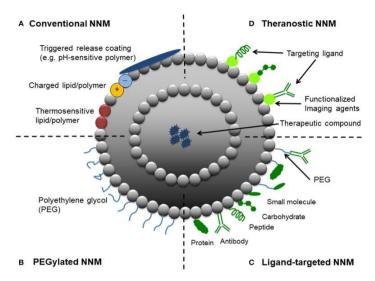


Figure 1: Schematic representation of different strategic designs for nanoparticulate noanomedicines (NNMs). (A)Conventional NNM—These NNMs can be modified with charged lipids/polymers, thermosensitive lipids/polymers and/or components for triggered release (e.g., pH-sensitive coating). (B) PEGylated NNM—Nanoparticle characteristics and behavior in vivo can be modified by the addition of a hydrophilic polymer coating, polyethylene glycol (PEG), to the NNM surface to confer steric stabilization. (C) Ligand-targeted NNM—Nanoparticles can be used for active targeting by attaching ligands (e.g., antibodies, peptides and carbohydrates) to its surface or to the terminal end of the attached PEG chains. (D) Theranostic NNM — These NNM systems consist of an imaging component and a therapeutic component, and may include a targeting element.

Scientists use nanotechnology to detect molecular biomarker for osteoarthritis (Felipe et al., 2018.)

This preclinical study used a solid-state nanopore sensor as a tool for the analysis of hyaluronic acid (HA). HA is a naturally occurring molecule that is involved in tissue hydration, inflammation and joint lubrication in the body. The abundance and size distribution of HA in biological fluids is recognized as an indicator of inflammation, leading to osteoarthritis and other chronic inflammatory diseases. It can also serve as an indicator of how far the disease has progressed.

Results established a new, quantitative method for the assessment of a significant molecular biomarker that bridges a gap in the conventional technology, The sensitivity, speed and small sample requirements of this approach make it attractive as the basis for a powerful analytic tool with distinct advantages over current assessment technologies.

304

The most widely used method is gel electrophoresis, which is slow, messy, semi-quantitative, and requires a lot of starting material. In this study, the researchers first employed synthetic HA polymers to validate the measurement approach. They then used the platform to determine the size distribution of as little as 10 nanograms (one-billionth of a gram) of HA extracted from the synovial fluid of a horse model of osteoarthritis.

The measurement approach consists of a microchip with a single hole or pore in it that is a few nanometers wide -- about 5,000 times smaller than a human hair. This is small enough that only individual molecules can pass through the opening, and as they do, each can be detected and analyzed. By applying the approach to HA molecules, the researchers were able to determine their size one-by-one. HA size distribution changes over time in osteoarthritis, so this technology could help better assess disease progression.

"By using a minimally invasive procedure to extract a tiny amount of fluid -- in this case synovial fluid from the knee -- we may be able to identify the disease or determine how far it has progressed, which is valuable information for doctors in determining appropriate treatments," we hope to conduct their next study in humans, and then extend the technology with other diseases where HA and similar molecules play a role, including traumatic injuries and cancer.



Figure 2: Nanotechnology-to-detect-molecular-biomarker-for-osteoarthritis.

Polymer nanoparticle shows ability to locate and treat breast tumors

H-DAPPs (Hybrid Donor-Acceptor Polymer Particles) are made of electrically conductive polymers and are smaller than 100 nanometers (0.00000393701 of an inch) in diameter. Their small size and soft composition makes it easy for them to travel through the bloodstream to the tumor. H-DAPPs a fluorescing nanoparticle capable of finding tumors, lighting up upon arrival and being activated with light to generate heat to destroy the cancer cells. They have

successfully located and killed breast cancer skills in mice is published in the current issue of the journal ACS Applied Materials and Interfaces. There is much more research needed to ensure that H-DAPPs can safely be used in humans, but we are enthusiastic about exploring the use of H-DAPPs with other cancer types and eventually in patients.



Figure 3: Hybrid Donor-Acceptor Polymer Particles.

Nanospears deliver genetic material to cells with pinpoint accuracy (Xiaobin Xu et al., 2018.)

Medical interventions based on the use of genetically modified cells are an emerging area of stem cell and cancer immunology research. Researchers have experimented with sharp-tipped nanoparticles stuck on surfaces to deliver biomolecules to cells, but it is difficult to remove the modified cells from the nanoparticle-coated surface. Self-propelled nanoparticles also can deliver molecules to cells in the body. However, these devices are difficult to precisely control and can generate toxic byproducts. To overcome these issues, Some researchers sought to create biocompatible nanospears that can be configured to transport DNA into cells precisely using an external magnetic field without either damaging the cells or having to use chemical propellants. The researchers fabricated nanospears using polystyrene beads as a template. They placed the beads onto silicon and etched them down into a tiny, sharp spear shape. The beads were removed, and the resulting silicon spears were coated with thin layers of nickel and gold. The gold was functionalized so that biomolecules, such as DNA, could attach. Then, the researchers removed the nanospears from the silicon by mechanical scraping. Because the nickel layer is magnetic, the particles' movement and orientation could be precisely controlled with a magnet. This capability allowed the researchers to maneuver the nanospears in a lab dish to modify brain cancer cells so that they expressed a green fluorescent protein. After making contact and penetrating the cells, the nanospears released their DNA cargo. After the experiment, more than 90 percent of the cells remained viable and more than 80 percent exhibited green fluorescence, showing that the method is less harmful and more effective than other non-viral approaches. The researchers conclude this technique could eventually lead to new ways to prepare vast numbers of cells for the coordinated manufacture of gene therapies.

Nanotech drug delivery shows promise for improved melanoma treatment (Bhuvana S.et al., 2015.)

Researchers have developed a new three-drug delivery system for cancer treatment, especially metastatic melanoma, the deadliest form of skin cancer -- and shown that the system may have particular value with cancers like this that often spread through the lymphatic system.

The new technology takes advantage of nanoparticles that can migrate to, and increase the effectiveness of an attack on cancer cells in the body's lymph nodes. This can also reduce the development of drug resistance and the broader toxicity often associated with this type of chemotherapy.

The findings were made with laboratory animals, and just published in the Journal of Controlled Release by researchers from the College of Pharmacy at Oregon State University. The work was supported by an OSU startup fund, and a provisional patent has been granted for this technology.

"Melanoma can be a very difficult cancer to treat because it often metastasizes and travels through the lymphatic system," said Adam Alani, an assistant professor in the Oregon State University/Oregon Health & Science University College of Pharmacy, and lead author on this research.

"Melanoma has a high mortality rate because the lymph nodes tend to act as a haven for cancer cells, and allow them to resist treatment through chemotherapy," he said.

The new OSU research, however, was able to combine three anti-cancer drugs at the same time into a nanoparticle delivery system. After injection, these nanoparticles primarily migrated to lymph nodes, acted in a synergistic manner that was more powerful than any one drug could be separately, and were able to maximize their impact in those locations while minimizing the development of drug resistance and overall toxicity.

Laboratory mice treated with this approach all survived. The therapy caused no apparent negative effects, and at least one type of the nanoparticles migrated effectively to distant lymph nodes, where the drugs significantly reduced the number of melanoma cells.

More research with animals, experiments with more aggressive forms of cancer, and eventually human clinical trials will still be needed for any treatment is available for use.

This could become an important advance in the treatment of any type of cancer that tends to move through the lymphatic system, Alani said. This includes melanoma, but also breast, head and neck, prostate, pancreatic, lung and gastric cancers.

Up to 80 percent of melanomas metastasize through the lymphatic system, the researchers said in their report, and the tumor cells even secrete growth factors to further streamline their progress. The enlarged lymphatic vessels "act as a freeway for the metastatic cells to gain access and spread to distal lymph nodes and organs," they wrote in the study.

The major drawback of existing therapies, they said, is the inability to deliver therapeutic concentrations of drugs to the lymphatic system without creating systemic toxicity. Use of drugs one at a time also tends to breed resistance to them.

The nanoparticles used to carry these cancer drugs are stable, increase the drug circulation time, and can deliver multiple drugs in a single step to the desired target, the research showed. They offer a novel therapeutic option for effective melanoma treatment, the scientists wrote in their conclusion.

Glowing' new nanotechnology guides cancer surgery, also kills remaining malignant cells (Olena Taratula et al., 2014.)

Researchers at Oregon State University have developed a new way to selectively insert compounds into cancer cells -- a system that will help surgeons identify malignant tissues and then, in combination with phototherapy, kill any remaining cancer cells after a tumor is removed. It's about as simple as, "If it glows, cut it out." And if a few malignant cells remain, they'll soon die.

The findings, published in the journal Nanoscale, have shown remarkable success in laboratory animals. The concept should allow more accurate surgical removal of solid tumors

at the same time it eradicates any remaining cancer cells. In laboratory tests, it completely prevented cancer recurrence after phototherapy.

Technology such as this, scientists said, may have a promising future in the identification and surgical removal of malignant tumors, as well as using near-infrared light therapies that can kill remaining cancer cells, both by mild heating of them and generating reactive oxygen species that can also kill them.

"This is kind of a double attack that could significantly improve the success of cancer surgeries," said Oleh Taratula, an assistant professor in the OSU College of Pharmacy.

"With this approach, cancerous cells and tumors will literally glow and fluoresce when exposed to near-infrared light, giving the surgeon a precise guide about what to remove," Taratula said. "That same light will activate compounds in the cancer cells that will kill any malignant cells that remain. It's an exciting new approach to help surgery succeed."

The work is based on the use of a known compound called naphthalocyanine, which has some unusual properties when exposed to near-infrared light. It can make a cell glow as a guide to surgeons; heat the cell to kill it; and produce reactive oxygen species that can also kill it. And by adjusting the intensity of the light, the action of the compound can be controlled and optimized to kill just the tumor and cancer cells. This research was done with ovarian cancer cells.

However, naphthalocyanine isn't water soluble and also tends to clump up, or aggregate, inside the body, in the process losing its ability to makes cells glow and generate reactive oxygen species. This also makes it difficult or impossible to find its way through the circulatory system and take up residence only in cancer cells.

OSU experts overcame these problems by use of a special water-soluble polymer, called a dendrimer, which allows the napthalocyanine to hide within a molecule that will attach specifically to cancer cells, and not healthy tissue. The dendrimer, an extremely tiny nanoparticle, takes advantage of certain physical characteristics that blood vessels leading to cancer cells have, but healthy ones do not. It will slip easily into a tumor but largely spare any healthy tissue.

Once in place, and exposed to the type of light needed, the cancer cells then will glow -creating a biological road map for a surgeon to follow in identifying what tissues to remove
and what to leave. At the same time, a few minutes of this light exposure activate the
naphthalocyanine to kill any remaining cells.

This one-two punch of surgery and a nontoxic, combinatorial phototherapy holds significant promise, Taratula said. It's quite different from existing chemotherapies and radiotherapies.

"For many cancers, surgery is a first choice of treatment," Taratula said. "In coming years we may have a tool to make that surgery more precise, effective and thorough than it's been before."

Before attempting human clinical tests, OSU researchers hope to perfect the process and then collaborate with Shay Bracha, an assistant professor in the OSU College of Veterinary Medicine, to test it on live dogs that have malignant tumors. The technique has already been shown successful in laboratory mice. Worth noting, the researchers said, is that even as phototherapy was destroying their malignant tumors, the mice showed no apparent side effects and the animals lost no weight.

Systems with technology similar to this are also being tested by other researchers, but some of them require several imaging and therapeutic agents, repeated irradiation and two lasers. This increases cost, may lessen effectiveness and increase risk of side effects, OSU researchers said in their report.



Figure 4: Dendrimer loaded with drug.

Facile Synthesis of Nanoparticles with Multiple Functions (Yang et al., 2009.)

Nanostructured materials have garnered great interest worldwide due to their unique sizedependent properties for chemical, electronic, structural, medical and consumer applications.

Singapore's Institute for Bioengineering and Nanotechnology (IBN) has discovered a new environmentally friendly method to synthesize a wide variety of nanoparticles inexpensively. This new chemical synthesis has been recently published in Nature Materials.

IBN researchers have developed a protocol to transfer metal ions from an aqueous solution to an organic solution such as toluene. Metal compounds that can dissolve in water are inexpensive and commonly available.

Many useful metals and scarce materials that are soluble in water may now become readily employed in the synthesis of nanoparticles. This new approach developed by IBN is a simple, room-temperature process that does not produce toxic chemicals.

The IBN research team has successfully transferred metal ions rapidly from water to an organic medium by mixing a solution of metal salts dissolved in water with an ethanol solution of dodecylamine (DDA). The metals would bond with the DDA and can then be extracted with organic solvent, chemical compounds that usually have a low boiling point, evaporate easily or can be removed by distillation. Solvents can be used to extract soluble chemical complexes from a mixture.

At IBN, the transfer of the metal ions from the aqueous phase to the organic phase was successfully applied towards the synthesis of a variety of metallic, alloy and semiconductor nanoparticles.

In contrast to other approaches for nanoparticles synthesis, the IBN protocol allows metalbased nanoparticles to be prepared in an organic medium using water-soluble, inexpensive, common metal precursors.

This method is highly efficient and easily applied to derive many types of nanoparticles that have interesting applications, including metal-semiconductor nanocomposites and hybrid nanoparticles.

Besides IBN's focus on applying this protocol to the nanocrystalline synthesis of metals, semiconductors and their hybrids, the extraction of metals dissolved in water would be significant for applications in environmental remediation, e.g. extraction of heavy metals from water and soil.

"Water pollution from heavy metals is a major long-term economic and healthcare problem that has global implications. Once contaminated, it is often difficult and expensive to purify the affected environment and extract the pollutants. Besides highly toxic metals such as mercury and lead, other valuable metals, including gold, silver, iridium and osmium, are also soluble in water, and may be extracted by our protocol," remarked IBN Research Scientist Jun Yang, Ph.D.

"At this point, it is possible to extract the metals very effectively using an organic solvent such as toluene to remove the metal residue. Organic solvents are less dense than ethanol or water and float on top of the aqueous solution. When we agitate the mixture, the metals dissolve in the toluene and are completely removed from the ethanol and water. Our process allows us to extract metals from water without leaching out the mineral ions that are normally present in water or soil," said Dr. Yang.

"We have demonstrated a general protocol for transferring metal ions from water to an organic phase. This technique may be applied to transfer a wide range of transition metal ions from water. We can greatly facilitate and reduce the cost of producing a variety of metallic, alloy, semiconductor and semiconductor-metal hybrid nanoparticles through our simple and flexible approach to engineer advanced materials with novel structures and multiple functionalities" said Jackie Y. Ying, Ph.D., IBN Executive Director and principal investigator of this research.

Nano-syringe delivers combination, targeted brain cancer therapy (Martyn A. et al., 2012.)

Nanomedicine researchers at the Methodist Neurological Institute and Rice University have developed a way to selectively kill brain cancer cells by using a tiny syringe to deliver a combination of chemotherapy drugs directly into the cells. These findings will be published in the April 24 issue of the American Chemical Society journal ACS Nano.

Patients with glioblastoma multiforme (GBM), the most common and aggressive malignant primary brain tumor, typically have a prognosis of 14-month median survival time despite medical interventions, which currently include surgery, chemotherapy and radiation.

The Rice-Methodist group developed the hydrophilic carbon cluster (HCC) antibody drug enhancement system (HADES), named after the Greek god of the underworld. Through a 20nanometer syringe, which is 2 million times smaller than a coffee mug, this nanovector successfully delivered a combination of three chemotherapy drugs into GBM cells in vivo, resulting in a high kill rate.

"Without our nano-delivery system, we know that current drug delivery would be highly toxic to patients if we tried to deliver all three of these drugs at once," said David Baskin, M.D., neurosurgeon at the Methodist Neurological Institute, who began his nanomedicine research in 2004 with the late Nobel laureate and Rice chemist Richard Smalley. "But delivered in combination using these nano-syringes, our research demonstrated extreme lethality, with at least a three-fold increase in the number of dead cancer cells following treatment. The nano-syringes selectively deliver these drugs only to cancer cells, and appear not to be toxic to normal neurons and other non-cancerous brain cells."

HCCs are nanovectors with protective antioxidant properties, capable of transporting and delivering drugs and bioactive molecules. In order to bring the drug carriers close enough to the cancer cells and successfully deliver the chemotherapy combination, three different antibodies were combined with the HCC to allow the nanoparticle to stick to the cell membrane. The drugs stayed inside the HCC until it attached to the cell membrane. Once binding occurred, the drugs were released into the fatty (lipid) environment in the membrane. The chemical properties of the chemotherapy drugs inside the HCC are such that they prefer to accumulate in areas with high concentrations of lipids and avoid areas with high water content, such as the extracellular space.

"A new and exciting advance is that now we have a carrier with protective properties, unlike previous nanotubes which were shown to be toxic," said Martyn Sharpe, the paper's lead author and a scientist with the Methodist NI's department of neurosurgery. "Some of the chemotherapy agents used in this research traditionally perform poorly with GBMs. Now that we've shown a successful kill rate of these cells in vivo, we're looking at treating human tumors that will be grown in immune-compromised mice models."

As personalized medicine continues to evolve, Baskin says this research could also be significant for other forms of cancer, including breast and head and neck cancers.

The paper represents an important collaboration between the laboratories of Baskin at Methodist, and James Tour, Ph.D. with Rice University's Smalley Institute for Nanoscale Science. Further work developing this system and expanding its utility is under way with continued collaboration between these two research groups.

The research was supported by The Henry J. N. Taub Fund for Neurological Research, The Pauline Sterne Wolff Memorial Foundation, Golfers Against Cancer, The Taub Foundation, The Verdant Foundation Limited and The Methodist Hospital Foundation.

Applications of nanoparticle systems in drug delivery technology-Nutraceutical Delivery (Rizvi Syed A.A. and Ayman M. Saleh., 2018.)

Nutraceuticals are food derived, standardized components with noticeable health benefits. They are commonly consumed as complement to various allopathic treatments as well as to provide extra health benefits and decrease risks of several chronic illnesses (Aggarwal et al., 2009). Similar to the case of any other drug, the bioavailability and thus efficacy of orally consumed nutraceuticals is affected by food matrices interactions, aqueous solubility, degradation/metabolism, and epithelial permeability (McClements et al., 2015). Most nutraceuticals are lipophilic molecules, such as fat-soluble vitamins (A, D, E and K), lipids other phytochemicals. Nanotechnology polyunsaturated and comprehensive assistance and most of the investigations have been aimed at improving the nutraceuticals via nanoparticle formulations dissolution mechanisms of 2009, McClements, 2015).

A large number of nutraceuticals, posse anti-inflammatory, antioxidative, antiapoptotic, and antiangiogenic activities, among those, the most prominent and studied is curcumin (diferuloylmethane). It is practically water-insoluble and has very poor bioavailability, thus various methods have been implemented to address this issue, such as liposomes, phospholipid vesicles, and polymer-based nano-formulation (Mohanty et al., 2010, Carvalho and Takeuchi et al., 2015). A 9-fold higher oral bioavailability of curcumin was observed when compared to curcumin co-administered with piperine (absorption enhancer) (Shaikh et al., 2009.). Another study of colloidal nanoparticles of curcumin dubbed, Theracurmin when compared to curcumin powder, exhibited 40-fold higher area under the curve (AUC) in rats

Swati et al.

and 27-fold higher in healthy human volunteers as well as inhibitory actions against alcohol intoxication (Sasaki et al., 2011).

Resveratrol is an important non-flavonoid polyphenol, naturally occurs in several plants but most abundantly found in Vitis vinifera, labrusca, and muscadine grapes (Celotti and Ferrarini, 1996.). It is known for antioxidant, cardioprotective, anti-inflammatory and anticancer activities (Summerlin et al., 2015). Resveratrol has low solubility, with decent bioavailability; however, it is rapidly metabolized and eliminated (Walle, 2011, Kapetanovic et al., 2011) from the body. There are two geometric isomers of resveratrol (cis- and trans), however the more abundant and bioactive trans-resveratrol, is photosensitive, converters to cis-resveratrol in the presence of light (Trela and Waterhouse, 1996). Many nanoformulations of resveratrol to improve the pharmacokinetic profile and bioavailability have been reported. These include polymeric nanoparticles (da Rocha Lindner and Bonfanti Santos, 2015, Sanna et al., 2013), Zein based nanoparticles (Penalva et al., 2015), nanoemulsions (Sessa et al., 2013), liposomes (Catania et al., 2013), cyclodextrins (Venuti et al., 2014), and dual nanoencapsulation methods (Soo et al., 2016). Recently, neuroprotective effects of Resveratrol were evaluated by preparing solid lipid nanoparticles decorated with apolipoprotein E for LDL receptor recognition on the blood-brain barrier (Neves et al., 2015).

CONCLUSION

Nanotechnology is truly a multidisciplinary science where chemists, physicist, biologists and pharmaceutical scientist all have played major roles to develop novel treatment and diagnosing modalities. It is evident through this review that application of nontechnology in drug delivery and medicine has paved new pathways and opened many doors for providing customizable and safer treatment option. The treatments of cancer and HIV/AIDS, non-invasive imaging as well as nutraceutical delivery have all progressed with the application of nanotechnology. Ultimately, through the manipulation of molecular size and surface properties, researchers are able to deliver drugs for longer period of time with less frequent dosing (sustained release) and with greater precision and penetration in difficult to access tissues.

Conflicts of interest: Nil.

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