Nanoparticles: the Future of Drug Delivery

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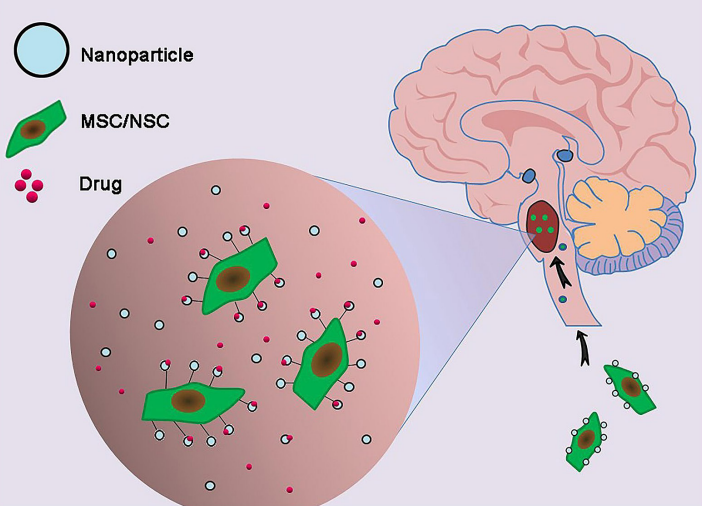
Drug development is one of the largest industries in the world. A significant amount of resources and time is invested into to produce drugs for clinical use. Equally important is the process of drug delivery and targeting by which the synthesized compounds are delivered to tissues in the body. As reported by Transparency Market Research in 2018, the drug delivery market is rapidly rising and is expected to be worth US $900 billion by 2025.

Drugs can be delivered into the body in multiple methods. These include topical, intranasal, oral, sublingual, and IV to mention a few. Following delivery, conventional drug targeting utilizes either direct targeting, in which the drug directly makes it way to the target tissue without carriers, or encapsulation method in which a drug is coated with molecules that act as carriers. However, these techniques have multiple limitations. The most substantial limitation is that these drugs cannot reach their target or are degraded en route. One of the hardest targets to reach is the brain as the blood-brain barrier is very restrictive making neurological targeting very difficult. Although it proves useful in protection against infection and hazardous chemicals, it is also very proficient at excluding medicine. Emerging drug delivery systems, like nanoparticles, show promise in overcoming the challenges faced by these traditional drug delivery methods.

Nanoparticles are defined by their size which is on the scale of 1 to 100 nm. In everyday language, if a human cell is imagined to be a football stadium, a nanoparticle would be a tennis ball on the field. Nanoparticles are quite diverse as they could be composed of organic compounds, such as carbon nanotubes, or inorganic materials, such as metallic ions. The type of material used influences stability and allows different drugs to be targeted.

This tiny size makes these particles distinct as they can provide exceedingly effective drug delivery to the remote regions within the human body. In addition, it allows nanoparticles to make the journey of drugs that are being carried by blood into the brain more efficient. Scientists at Cedars-Sinai Medical Center developed a nanoparticle that can cross the blood brain barrier in a mouse to deliver drugs with high specificity. The authors further indicated that the conjugated nanoparticles, nanoparticles connected other molecules, cross the blood brain barrier more efficiently than traditional methods. Furthermore, conjugating molecules that have a high affinity for different brain tissues can further increase delivery across the blood brain barrier.

However, challenges remain in nanoparticle-based brain targeting. Israel L. et al (2019) noted that nanoparticle delivery is dependent on the presence of blood vessels in close proximity to the targeted tissue. The lack of vessels of certain regions of the brain makes them virtually inaccessible by nanoparticles. The researchers have now begun to focus on the nanoparticle delivery to these inaccessible regions.



Nanoparticle diagram attributed to W. Long, Y. Yi, S. Chen, Q. Cao, W. Zhao and Q. Liu [CC BY 4.0].

Nanoparticles can even target different organelles within the cell. The particles have the potential to penetrate within the cellular structure and reach as far as the nucleus, where the genetic material of the cell is housed as shown by researchers at the University of Science and Technology of China. Using a modified nanoparticle which includes a C_5N_2 group and a nuclear localization signal that helps to increase stability and direct toward the nucleus, respectively. Chen et al (2019) found that this particle was not only capable of delivering molecular dyes and drugs to the nucleus but could provide enhanced antitumor capacities in mice compared to conventional chemotherapy and non-nucleus targeting nanoparticle chemotherapy. The researchers believe this new targeting methodology may open door for the development of therapy with enhanced antitumor activity.

Currently the mitochondria, the main energy source of the body, remains one of the most difficult structures to target inside the cell. Many mitochondrial pathologies exist have debilitating consequences. For example, mitochondrial myopathy, a neuromuscular disease caused by damage to the mitochondria, causes a multitude of symptoms including heart failure and deafness. These pathologies are essentially incurable due to the difficulty in mitochondrial targeting. The promising results of nanoparticle based nuclear targeting may translate to mitochondrial targeting hence the focus of many nanoparticle-focused laboratories around the world.

The use of nanoparticles for drug delivery systems is not without its challenges. Despite the advantages, a relatively small number of nanoparticles have been approved for clinical use. The biggest hurdle impeding nanoparticle-based targeting is the complexity in designing the multicomponent three-dimensional constructs. For example, detailed understanding of the components and their interactions in cellular structures is required before nanoparticle-based medicine can be used in the clinical setting.

Furthermore, nanoparticles come in many flavors; physical characteristics such as size, shape, surface area, and volume vary significantly between individual particles. Finding the correct particle for the intended use plays an important role in targeting drugs efficiently and reducing side effects. For example, one nanoparticle may be useful in targeting only a subset of drugs with particular chemical properties while other nanoparticles make require additional stabilizing compounds for drug trafficking . Therefore, finding the correct particle for a particular drug can prove to be quite challenging and often proves to be the bottleneck in nanoparticle-based drug trafficking research.

Another major challenge researchers face is the delivery of nanoparticles to solid tumors. Tumor microenvironments are highly complex and heterogeneous with variable vasculature - the distribution of blood and lymph vessels around the tumor. Certain large solid tumor regions, especially the core, are poorly vascularized. As a result, the passage of nanoparticles to these regions is heavily limited. Furthermore, the presence of dense collagen, a mesh of gelatinous protein, trap any further nanoparticles, preventing them from making their way deeper into the tumor. As a result of these setbacks, current research in the field of nanoparticles-based tumor drug delivery is now focused on “active” targeting of nanoparticles to the target rather than the traditional “passive”. By conjugating antibodies that have affinity for specific regions in the body, researchers hope to actively target the inaccessible tumor regions onto the particles rather than passively relying on nanoparticles to reach the target by themselves.

Despite these challenges, nanoparticles hold a lot of potential for drug delivery. The development of better and more predictive pre-clinical animal models coupled with a better understanding of biology can help improve the nanoparticle-based drug targeting. Ultimately, cross collaboration with theoretical and experimental scientists across academia, medicine, and the pharmaceutical industry will help translate findings from the lab to better ways to target diseases.

REFERENCES

Chen, W., Liu, J., Wang, Y., Jiang, C., Yu, B., Sun, Z., Lu, L. (2019). A C_5N_2 Nanoparticle Based Direct Nucleus Delivery Platform for Synergistic Cancer Therapy. *Angewandte Chemie International Edition*, 58 (19), 6260-6294, available: https://doi.org/10.1002/anie.201900884.

Israel, L. L., Braubach, O., Galstyan, A., Chiechi, A., Shatalova, E. S., Grodzinski, Z., Ding, H., Black, K. L., Ljubimova, J. Y., Holler, E. (2019). A Combination of Tri-Leucine and Angiopep-2 Drives a Polyanionic Polymalic Acid Nanodrug Platform Across the Blood–Brain Barrier. *ACS Nano*, 13(2), 1253-1271, available: https://doi.org/10.1021/acsnano.8b06437.

Rosemblum, D., Joshi, N., Tao, W., Karp, J. M., Peer, D. (2018). Progress and challenges towards targeted delivery of cancer therapeutics. *Nature Communications*, 9, 1410, available: https://www.nature.com/articles/s41467-018-03705-y.

Tiwari, G., Tiwari, R., Sriwastawa, B., Bhati, L., Pandey, S., Pandey, P., Bannerjee, S. K. (2012). Drug delivery systems: An updated review. *International Journal of Pharmaceutical Investigation*, 2(1), 2–11, available: http://www.jpionline.org/index.php/ijpi/article/view/58.