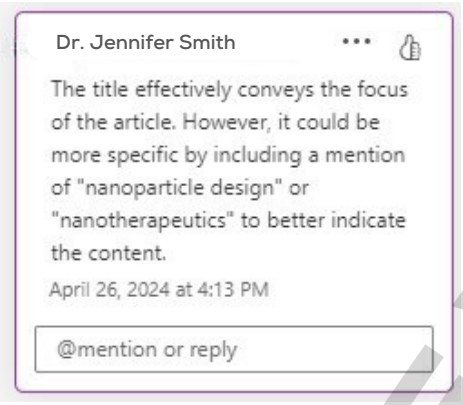
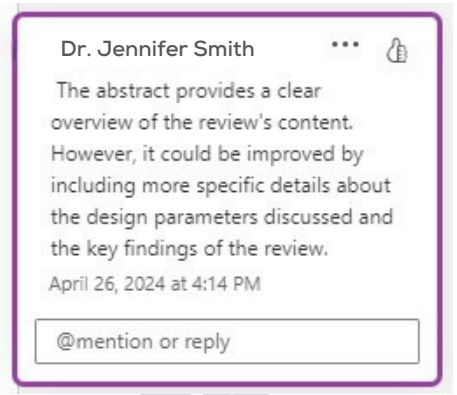
Design Considerations for Nanotherapeutics in Oncology

Summary:

The article provides a comprehensive review of the design considerations for nanotherapeutics in oncology. It discusses the status of clinically approved nanoparticles, their limitations, and strategies to improve drug delivery and treatment efficacy. The authors highlight the importance of active tumor targeting and drug release rate in optimizing intratumoral delivery. The review also suggests specific design strategies for enhancing delivery to solid tumors.





Abstract :

Nanotherapeutics have improved the quality of life of cancer patients, primarily by reducing the adverse effects of chemotherapeutic agents, but improvements in overall survival are modest. This is in large part because the enhanced permeability and retention effect, which is the basis for the use of nanoparticles in cancer, can be also a barrier to the delivery of nanomedicines. A careful design of nanoparticle formulations can overcome barriers posed by the tumor microenvironment and result in better treatments. In this review, we first discuss strengths and limitations of clinically approved nanoparticles. Then, we evaluate design parameters that can be modulated to optimize delivery. The benefits of active tumor targeting and drug release rate on intratumoral delivery and treatment efficacy are also discussed. Finally, we suggest specific design strategies that should optimize delivery to most solid tumors and discuss under what conditions active targeting would be beneficial.

From the Clinical Editor :

Advances in nanotechnology have seen the introduction of new treatment modalities for cancer. The principle of action using nanocarriers for drug delivery is based mostly on the Enhanced Permeability and Retention effect. This phenomenon, however, can also be a hindrance. In this article, the authors performed an in-depth review on various nanoparticle platforms in cancer therapeutics. They also suggested options to improve drug delivery, in terms of carrier design.

Graphical Abstract

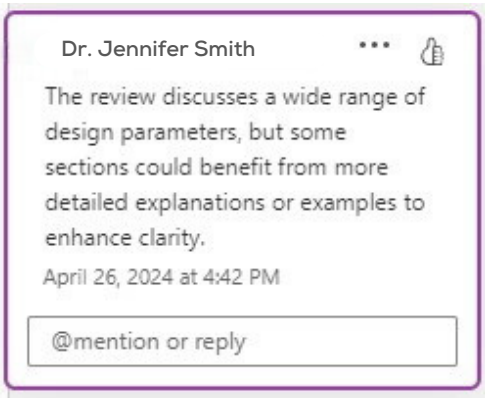
Barriers posed by the abnormal tumor micro-environment hinder delivery of nanoparticles to solid tumors, causing heterogeneous drug distribution and reducing the efficacy of the treatment. Careful design of the physicochemical properties of nanoparticles, their binding affinity to cancer cells, and the controlled release of the drug can improve delivery and treatment outcomes. In this review, design considerations are provided for nanotherapeutics in oncology. Image shows heterogeneous intratumoral distribution of liposomes (bright red color) 90 nm in diameter (with permission from Yuan, F. et al Cancer Res. 54, 3352-3356, 1994).

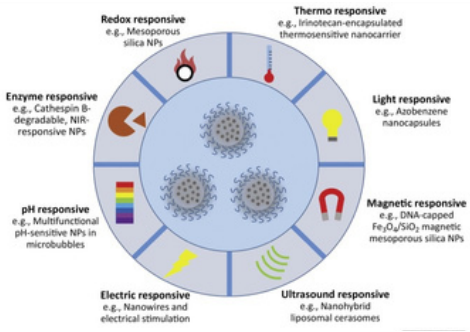
Cancer nanomedicines in clinical use and in trials:

Currently, clinically approved cancer nanomedicines make use of the EPR effect, i.e., passive accumulation into the tumor, and include (Figure 1): Doxil (or Caelyx) – an ~ 100 nm PEGylated liposomal doxorubicin particle – approved for the treatment of HIV-related Kaposi's sarcoma, metastatic ovarian cancer and metastatic breast cancer; DaunoXome – a 50 nm liposomal daunorubicin particle – approved for HIV-related Kaposi's sarcoma; Myocet – an 150-180 nm non-PEGylated liposomal doxorubicin particle.

Design considerations :

Delivery of blood-borne therapeutic agents to solid tumors is determined by the circulation time of the particles within the vascular network, the ability of the particles to cross the tumor vessel wall into the tumor interstitial space, the interstitial transport of the particles within the tumor and in some cases their internalization by cancer cells.3, 8





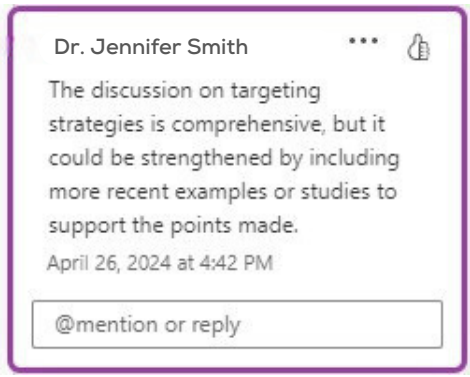
Multifunctional and stimuli-responsive drug delivery systems :

Nanoparticle delivery systems apart from acting as drug-carriers might have other functions as well.107 Such functions often involve the controlled release of the therapeutic agent from the nanoparticle, employment of targeting agents (e.g., antibodies, peptides) for specific binding of the particles to cancer cells or other target in the tumor microenvironment or an imaging agent for diagnostic purposes.108, 109, 110, 111, 112, 113, 114 Furthermore to trigger drug release, nanoparticles might

Targeted nanomedicines: the interplay among interstitial diffusion, drug release rate and binding affinity :

For the case of targeted nanoparticles, additional design considerations are necessary. Once the nanoparticle enters the tumor interstitial space.

a competition of three mechanisms determines its efficacy: i) the penetration of the nanoparticle into the tumor, described primarily by its interstitial diffusivity, D, ii) the rate of release of the anti-cancer drug, described by the release rate constant, Krel, and iii) the binding affinity of the nanoparticle or the released drug to cancer cells,

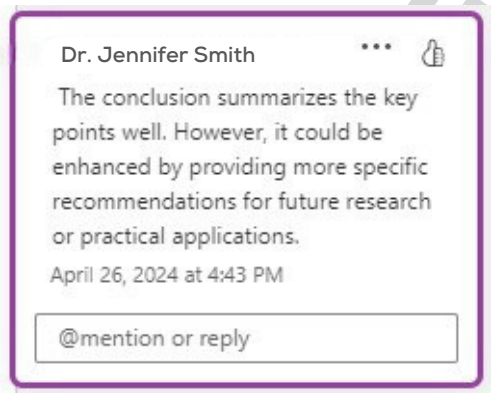


Design strategies to optimize delivery

A summary of the design guidelines described in the previous sections is presented in Table 3. Along with this information, which deals with the delivery aspect, we need to consider the drug loading and release rate of the nanoparticle and its targeting capability (Figure 4). As this review focuses on the optimal delivery of nanoparticles, we propose three different design strategies.

Closing remarks :

In our analysis we focused on the effect of the physical properties of nanoparticles, and we considered passive delivery through the EPR effect. Stimuli responsive nanoparticles exist that respond to an internal stimulus of the tumor microenvironment such as pH, temperature, enzyme activity, Redox or an external source and particularly to a magnetic field, ultrasound, heat or light. The stimulus is used either to increase the concentration of the nanoparticles in the tumor site or to locally



Comments:

1.Strengths:

- The article provides a detailed overview of clinically approved nanoparticles, which will be informative for researchers and clinicians in oncology.
- The discussion on design parameters for optimizing nanoparticle delivery is well-structured and offers practical insights for improving treatment outcomes.

2.Areas for Improvement:

- While the review focuses on passive delivery through the Enhanced Permeability and Retention (EPR) effect, it would be beneficial to discuss the potential of stimuli-responsive nanoparticles in more detail.
- The review could benefit from including recent advances in nanotechnology that have impacted the field of oncology, such as the development of novel drug delivery systems and imaging agents.

2.Additional Comments:

- The graphical abstract and image provided in the article are visually appealing and effectively illustrate the concepts discussed in the review.
- The closing remarks could be strengthened by discussing future directions and emerging trends in nanotherapeutics for oncology.

Recommendation:

Overall, the article provides valuable insights into the design considerations for nanotherapeutics in oncology. With some revisions to address the areas for improvement, it has the potential to be a highly impactful contribution to the field. I recommend accepting the article pending minor revisions.