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It may all come down to the mechanisms of nanoparticle delivery

A long-standing nanoparticle delivery paradigm in cancer, that is, the enhanced permeability and retention effect, has been challenged, shifting the focus to active delivery mechanisms, which may provide a new mechanistic foundation for nanoparticle design.

Nanoparticles can deliver drugs into tumours following systemic injection. This key assumption provides the foundation and justification for cancer nanomedicine, exploring a vast number of nanoparticles, with different sizes, shapes and materials, as drug delivery vehicles — at least in the scientific literature. Here, targeted delivery is important because systemically administered nanoparticles cannot function as designed if they do not reach and access the diseased cells and tissues at a sufficiently high dosage. Underlying this assumption has long been a mechanism called the enhanced permeability and retention (EPR) effect, which states that nanoparticles passively enter the tumour through gaps between endothelial cells (owing to leaky tumour vasculature) and are retained because of poor lymphatic drainage[1]. Assuming this mechanism, nanoparticle design has mainly focused on size (its size should be smaller than the size of interendothelial gaps) and circulation time (to ensure that accumulation can occur despite clearance), in addition to tumour targeting (to reduce accumulation in other tissues) and multifunctionality.

Yet, the clinical translation of nanoparticle-enabled cancer treatments has been modest thus far, a fact heavily debated — and not yet resolved — in the cancer nanomedicine community[2–4].

The limited efficacy of cancer-targeted nanoparticles may be a result of tumour heterogeneity, variable pathophysiology between tumour models, animals and human patients, complexities of nanoparticle designs, as well as the lack of patient stratification. Adding to these factors, recent studies suggest that mechanisms in addition or alternative to the EPR effect may be at play here.

Warren Chan and team recently proposed an active delivery mechanism, called the active transport and retention (ATR) principle, suggesting that nanoparticles enter the tumour through active endothelial transport processes, are retained owing to interactions with tumour components and exit the tumour through lymphatic vessels[5,6]. In this issue, Chan and colleagues discuss how the ATR principle may provide guidance for engineering nanoparticle entry, exit and retention processes, without relying solely on leaky vasculature and lymphatics. Of note though, the ATR principle was established using gold, silica and liposome nanoparticles, and it remains to be validated for other nanoparticle types. Moreover, several mechanistic key questions remain to be addressed, as outlined in this issue. Thus, the ideal nanoparticle for cancer applications remains yet to be sketched.

> "... recent studies suggest that mechanisms in addition or alternative to the EPR effect may be at play"

It will also be key to investigate the mechanisms influencing blood circulation, biodistribution and tissue accessibility for different nanoparticle platforms to control their biodistribution and clearance, as discussed by Kazunori Kataoka and colleagues in this issue. Of note, nanomedicine-relevant pharmacodynamics and pharmacokinetics definitions are currently being developed, together with engineering strategies to modulate these parameters. The ATR principle now adds to this toolbox; for example, nanoparticle entry may be increased by stimulating the active transport of nanoparticles by vesiculo-vacuolar organelles; their exit may be minimized by reducing tumour lymphatic flow; and their retention may be controlled using extracellular matrix crosslinking or degrading proteins.

However, before the next wave of new nanoparticle designs enters the literature, it may be wise to first investigate the detailed mechanisms of active transcytosis underlying the ATR principle and identify the factors that trigger this transport process — for different nanoparticle types and materials. Furthermore, improving nanoparticle delivery efficiency is only one side of the coin. Heterogeneity of tumours and differences between patients, as well as between patients, animal models and in vitro testing systems, remain a translational hurdle to nanoparticle-based cancer applications. Nevertheless, the more mechanistic insight, the closer we may get to engineering nanoparticles that actually reach the clinic, moving from nanoparticle designs that are 'publishable' to platforms that are 'translatable'.

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References

1. Matsumura, Y. & Maeda, H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. *Cancer Res.* **46**, 6387–6392 (1986).
2. Park, K. The drug delivery field at the inflection point: Time to fight its way out of the egg. *J. Control. Release.* **267**, 2–14 (2017).
3. The two directions of cancer nanomedicine. *Nat. Nanotechnol.* **14**, 1083 (2019).
4. van der Meel, R. et al. Smart cancer nanomedicine. *Nat. Nanotechnol.* **14**, 1007–1017 (2019).
5. Nguyen, L. N. M. et al. The exit of nanoparticles from solid tumours. *Nat. Mater.* **22**, 1261–1272 (2023).
6. Sindhwani, S. et al. The entry of nanoparticles into solid tumours. *Nat. Mater.* **19**, 566–575 (2020).