LINK TO ORIGINAL ARTICLE
LINK TO AUTHOR'S REPLY

Evaluation of nanomedicines: stick to the basics

Scott E. McNeil

The Perspective by Chan and co-workers, (Analysis of nanoparticle delivery to tumours, *Nat. Rev. Mater.* **1**, 16014 (2016))[1] continues an important discussion on the effectiveness of nanoparticle-based therapeutics. I note, however, that this retrospective study relies heavily on an unconventional parameter to assess the success or failure of nanomedicine; namely, the average amount of detectable nanoparticle carrier present over time in the tumour tissue.

At the Nanotechnology Characterization Laboratory (NCL), we have conducted over 150 extensive pharmacokinetic (PK) and toxicological preclinical studies for proprietary nanomedicines. NCL studies have found that the 'nanoparticle in tumour' parameter does not serve as a good surrogate for therapeutic index, nor does it govern regulatory approval of nanoformulations[2]. In contrast to the analysis used by Chan and co-workers, evaluation of the nanoparticle's active pharmaceutical ingredient (API; that is, the drug) is the far more relevant consideration and is required to compare critical factors such as PK, toxicity and efficacy among formulations.

Traditional PK parameters, such as peak drug concentration (C_{max}), clearance rate from the body (CL), elimination half-life ($t_{1/2}$) and volume of distribution (V_d), provide comparative information on the effects imposed on the API by the nanoformulation[3]. The C_{max} of the API, for example, helps determine if an adequate cancer-killing dose reaches the tumour. The method selected in the Perspective involves the calculation of an average nanoparticle concentration, which precludes evaluation of these important PK parameters. The API exists in encapsulated, free and protein-bound forms. Free API is the bioactive form that can induce a cancer-killing effect. The only aim of the Perspective was to measure the encapsulated form, with the assumption that the drug remains with the nanoparticle. The authors also erroneously interchange nanoparticle and API area under the curve results in their calculations, which we infer from the experimental design and experimental data in the cited references. These oversights highlight the ambiguity of their 'nanoparticle in the tumour' premise and inferences.

Accumulation in the tumour is certainly an important problem for nanomedicines that rely on an external stimulus. Nanoparticles that contain an imaging agent and/or have a non-chemical mechanism of action (for example, laser-induced thermal ablation), require a sufficient concentration of particles in the tumour to transduce the stimulus into a cytotoxic action. In the case of nanoparticle-delivered small molecule drugs, it seems intuitive that the more nanoparticles there are in the tumour tissue, the more drug is delivered. However, it is misleading to place undue importance on this one parameter in lieu of classical pharmacological evaluation of drugs.

Liposomal doxorubicin (Doxil) is a historical example to bring further clinical perspective to the authors' assumptions. For Doxil, less than 1% of the injected dose is detectable in the tumour, yet this is many times greater than an equivalent dose of traditionally formulated doxorubicin[4,5]. Clinically, liposomal doxorubicin also dramatically enhances the length of tumour exposure with a $t_{1/2}$ that is nearly fivefold greater and a CL that is three orders of magnitude slower than traditionally formulated doxorubicin. These combined effects bestow an improved anticancer treatment for patients with significantly reduced cardiotoxicity[6].

The Doxil example points out how nanoformulations can advantageously alter the PK and toxicity profile of a drug to improve the quality of life for the patient. But why have we not seen huge improvements in clinical efficacy for nanomedicines and dramatic increases in survival rates? To date, the majority of nanoparticle-based therapies in clinical trials incorporate off-patent cytotoxic agents to de-risk regulatory evaluation. Despite the reformulation, it is still the same API with the same cellular mechanism of action and the same potential for drug resistance. One should not expect remarkable improvements in efficacy if the cytotoxic agent is unchanged. That said, the pharmaceutical industry is now marrying potent novel drugs with nanoparticles early in the preclinical phase and taking into account relevant structure–activity relationships during the development stage[7]. The resulting nanoformulations are intended for first-in-man studies, thus we anticipate advances in clinical efficacy as these progress to phase II and III trials.

Regarding clinical translation, the statement "…we have not observed significant clinical translation of cancer nanomedicines" is quickly rebutted by empirical evidence. According to Clinicaltrials.gov, a search on 5 August 2016, using "(nanoparticle OR liposome OR micelle) AND cancer" yields over 500 clinical studies, with nearly 25% of those in Phase III trials. Celator Pharmaceuticals is a relevant case study in this regard. The company recently completed their phase III trial on CPX-351 (VYXEOS), a nanoparticle formulation of cytarabine and daunorubicin. The nanoparticle carrier allows the drugs to be co-administered at a fixed, optimal ratio. In patients with high-risk acute myeloid leukemia (AML), CPX-351 revealed a 31% reduction in the risk of death compared with the standard of care regimen for the two drugs. With respect to mean overall survival, AML patients treated with CPX-351 lived 9.56 months compared with 5.95 months for the legacy combination[8]. Celator is being acquired by Jazz Pharmaceuticals for US$1.5 billion[9].

In summary, the overarching goal of nanomedicine is to improve patient outcomes. As indicated above, nanoformulations now have a clinical track record for improving the PK profile of a drug and decreasing toxicity. Evaluating nanomedicine solely on the basis of the %ID of nanoparticles that reach the tumour is unconventional and has led the authors to a conjecture that is inconsistent with the observed clinical results. The parameters used in measuring the success of nanomedicine translation to the clinic should include considerations of pharmacokinetics, toxicity, efficacy and the overall impact on patient outcomes.

Scott E. McNeil is with the National Cancer Institute's Nanotechnology Characterization Laboratory at the Frederick National Laboratory for Cancer Research, Frederick, Maryland 21702, USA.
ncl@mail.nih.gov

Published online 13 Sep 2016

1. Wilhelm, S. *et al.* Analysis of nanoparticle delivery to tumours. *Nat. Rev. Mater.* **1**, 16014 (2016).
2. Tyner, K. & Sadrieh, N. Considerations when submitting nanotherapeutics to FDA/CDER for regulatory review. *Methods Mol. Biol.* **697**, 17–31 (2011).
3. Brunton, L. L., Chabner, B. & Knollmann, B. C. *Goodman & Gilman's the Pharmacological Basis of Therapeutics* (McGraw-Hill Medical, 2011).
4. Laginha, K. M., Verwoert, S., Charrois, G. J. & Allen, T. M. Determination of doxorubicin levels in whole tumour and tumour nuclei in murine breast cancer tumours. *Clin. Cancer Res.* **11**, 6944–6949 (2005).
5. Gabizon, A. *et al.* Long-circulating liposomes for drug delivery in cancer therapy: a review of biodistribution studies in tumour-bearing animals. *Adv. Drug Deliv. Rev.* **24**, 337–344 (1997).
6. Safra, T. *et al.* Pegylated liposomal doxorubicin (doxil): reduced clinical cardiotoxicity in patients reaching or exceeding cumulative doses of 500 mg/m^2. *Ann. Oncol.* **11**, 1029–1033 (2000).

7. Blanchard, F. Collaboration with pharma will introduce nanotechnologies in early stage drug development. *Leidos Biomedical Research* https://leidosbiomed.wordpress.com/2016/06/03/collaboration-with-pharma-will-introduce-nanotechnologies-in-early-stage-drug-development/ (2016).
8. Lancet, J. E. *et al.* Final results of a phase III randomized trial of CPX-351 versus 7 + 3 in older patients with newly diagnosed high risk (secondary) AML. *J. Clin. Oncol.* **34** (Suppl.), abstr. 7000 (2016).
9. [No authors listed.] Jazz Pharmaceuticals And Celator Pharmaceuticals Announce Agreement For Jazz Pharmaceuticals To Acquire Celator For $30.25 Per Share. *PR Newswire* http://www.prnewswire.com/news-releases/jazz-pharmaceuticals-and-celator-pharmaceuticals-announce-agreement-for-jazz-pharmaceuticals-to-acquire-celator-for-3025-per-share-300276751.html (updated 31 May 2016).

Acknowledgements
Funded by NCI Contract No. HHSN261200800001E.

Competing interest statement
The author declares no competing interests. Celator Pharmaceuticals, Inc. is a former NCL collaborator.