REPLY

Reply to "Evaluation of nanomedicines: stick to the basics"

Stefan Wilhelm[1], Anthony J. Tavares[1] and Warren C. W. Chan[1,2,3]

McNeil has captured the main criticism of our Perspective article (Analysis of nanoparticle delivery to tumours. *Nat. Rev. Mater.* **1**, 16014 (2016))[1] in his Correspondence (Evaluation of nanomedicines: stick to the basics. *Nat. Rev. Mater.* http://dx.doi.org/10.1038/natrevmats.2016.73 (2016))[2]. A major flaw of his argument is associated with the number of clinical studies. McNeil's "empirical evidence" suggests that there are "over 500 clinical studies, with nearly 25% of those in phase III trials". At first sight, these numbers are impressive and might indicate that significant clinical translation and the success of cancer nanomedicine developments are a reality.

We used McNeil's search terms and analysed the results from the Clinicaltrials.gov database in detail (Supplementary information S1–S3 (box, figure, table); FIG. 1). The database query resulted in 582 ongoing (open and closed, active not recruiting) clinical studies. To our surprise, 339 (>58%) of these studies do not use any nanotechnology-based drugs and are therefore irrelevant to the discussion (FIG. 1a). The keyword list of these 339 irrelevant studies contained at least one of McNeil's search terms. It is unclear to us why this is the case. The real number of relevant studies from McNeil's database query is 243, with 42 (17%) and 3 (1%) formulations in phase III and IV trials, respectively (FIG. 1b). None of these phase III and IV studies uses actively targeted cancer nanomedicine. All three phase IV studies are focused on liquid tumour treatment rather than solid tumours. In our Perspective, we explored and discussed the issues of nanoparticle delivery to solid, not liquid, tumours. Furthermore, ~75% of the relevant clinical trials are reformulations of US Food and Drug Administration (FDA)-approved drugs, such as abraxane or liposome-encapsulated known drugs (that is, repurposed nanoformulations), using nanoformulation chemistries from 20 to 40 years ago (FIG. 1c). Moreover, a meta-analysis by La-Beck and co-workers showed that the anticancer efficacy of liposome-based chemotherapy formulations from 14 clinical trials was not different from conventional chemotherapies, in contrast to studies in mice[3]. McNeil further speculates that "potent new drugs" will address the therapeutic-efficacy problem of nanomedicines. This would suggest that novel, active pharmaceutical ingredients would be the main drivers for improved therapeutic response rather than nanotechnology itself.

McNeil further suggests that the acquisition of Celator by Jazz Pharmaceuticals for US$1.5 billion provides evidence of the field's success. Using his logic, we can state that the field has failed, as there are actually more failures than success stories. In 2007, Merck purchased Sirna Therapeutics for $1.1 billion[4], and there are no siRNA-based drugs currently on the market. Merck later sold that research division to Alnylam for $175 million[5] — a loss of $925 million. This loss of financial value does not mean that the proposed siRNA delivery is unrealistic, as there are many possible reasons why the technology failed at that time. When flagship companies such as BIND Therapeutics fail (sold for $40 million despite a maximum market capital of over $230 million), it negatively affects the entire research community beyond investors, founders and employees. If Celator (now Jazz Pharmaceuticals) is able to advance their technology for regular patient treatment, the community will cheer, as this will translate into significant optimism within the entire field. At this point, it is important to monitor the progress of Celator, at both scientific and business levels, to generate a model for other cancer nanomedicine developments. The success of Celator might be a result of their chosen diseased target (that is, liquid tumours), nanoformulation design or other factors. We need to acknowledge that the success of our research field is only real if we can see achievements at all levels: in academia (in the form of publications); in companies (in the form of clinically used products); and ultimately in the clinic (with therapeutic benefits for patients).

The use of standard pharmacokinetic (PK) metrics, as suggested by McNeil, is currently not an option for a detailed analysis of cancer nanomedicines. Our literature survey showed that very few researchers report these metrics for their studies. A potential reason for this is that PK metrics describe the accessible concentration of the drug in the blood (or plasma)[6]. From a nanoformulation perspective, these metrics are disputable. For example, doxorubicin encapsulated in liposomes may not be bioavailable to target DNA and/or generate reactive oxygen species. Therefore, measurements of the peak drug concentration (C_{max}) of doxorubicin may be inappropriate when nanocarriers are used. Many cancer-nanomedicine developments focus on the nanoparticle itself rather than the drug. Consequently, researchers report the quantification of these nanoparticles at the target site (that is, the tumour). In our Perspective, we used the available published data to calculate the delivery efficiency of nanocarriers to solid tumours to enable a standardized comparative analysis. Researchers have the opportunity

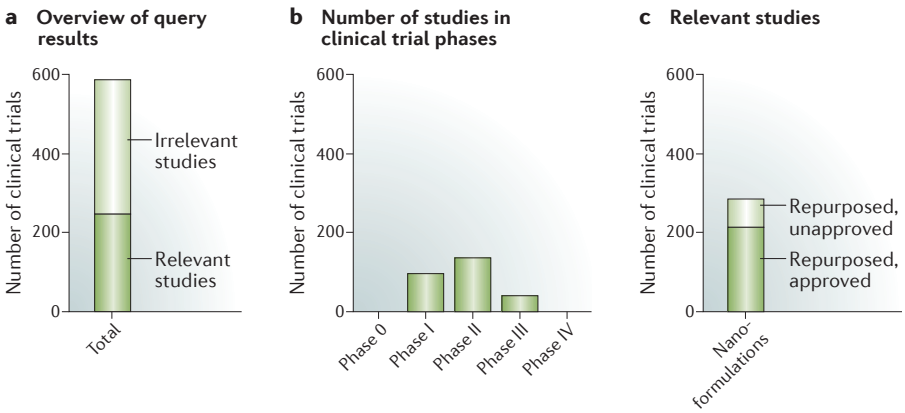

Figure 1 | **Analysis of studies in clinical trial phases. a** | Clinicaltrials.gov database query resulted in 582 ongoing (open and closed, active not recruiting) clinical studies (performed on 16 August 2016); 339 studies were irrelevant. **b** | Distribution of relevant studies with respect to clinical trial phases. **c** | Approximately 75% of relevant clinical studies are reformulations of US Food and Drug Admisistration (FDA)-approved drugs, such as abraxane or liposome-encapsulated known drugs (that is, repurposed nanoformulations). Further detailed breakdown of the clinical trials (according to material, targeting strategy, tumour type, application and novelty) is described in the Supplementary information S1–S3 (box, figure, table).

to access and re-analyse the raw data of our Perspective's analysis, which is summarized in 138 pages of Supplementary information. To determine the best metric to assess the nanomedicine performance, one has to compare the therapeutic effectiveness against the method of analysis. This is currently not possible because of a lack of standardization among methods. The FDA has not established a regulatory framework for nanomedicine.

We consider that the field of nanomedicine will be strong when there is a broad range of real success stories from academia, companies and the clinic (which is currently not the case), rather than when anecdotes are told or, in some cases, successes from other fields (such as antibody-based drugs) are included as part of nanotechnology. Our analyses of the nanomedicine-delivery efficiency, and now nanomedicine clinical trials, suggest that many published studies provide interesting concepts in cancer nanomedicine, but most of these concepts do not advance beyond the academic laboratory. Nanoparticle-to-tumour delivery efficiency is likely to be the first part of the problem, as the intratumoural kinetics, interactions and fate of nanomedicines are also important for the use of nanomedicine in cancer applications. The literature lacks sufficient studies to make a full evaluation in this regard. Recognizing the limitation of nanoparticle delivery, our group has started to evaluate the idea of personalized nanomedicine that takes into account tumour variability and heterogeneity. In this concept, nanoparticles are designed based on the tumour properties (for example, collagen densities)[7]. This idea goes beyond the one-size-fits-all tumour-targeting model. To validate the feasibility of this concept, we had to use animal models, as this cannot be done in patients with cancer. Thus, we consider our effort to be a success story from a publishing perspective but not from a patient perspective. Vast resources and energy are needed to make this concept a reality in the clinic. Moving forward, we challenge the community to refocus and redefine the objectives of cancer nanomedicine, which could include: altered toxicological profiles; improved nanomedicine-delivery efficiency to tumours; improved therapeutic outcomes; or increased imaging contrast. The objective has to be tailored to the selection of proper diseased or biological targets. Furthermore, we challenge the community to use a data-driven approach to identify problems and challenges, and to develop a streamlined, rational and mechanistic strategy to the translation process. One of the first steps initiated by our group is the launch of the Cancer Nanomedicine Repository, which is an online and open-access database to monitor the progress in the field. These efforts may enable us to increase the probability of clinical success for nanomedicine. The ability of the community to get this translation process right will have enormous implications on our society. Ultimately, this will result in patient benefits. However, it can only be accomplished by collective and concerted efforts of an entire research community with clearly defined objectives.

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Competing interests statement
The authors declare no competing interests.

DATABASES
Cancer Nanomedicine Repository: http://inbs.med.utoronto.ca/cnr
Clinicaltrials.gov: https://clinicaltrials.gov/

SUPPLEMENTARY INFORMATION
See online article: S1 (box) | S2 (figure) | S3 (table)

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