

**Cover story****Translation from mouse to human: Time to think in new boxes**

This issue presents 6 articles describing targeted drug delivery using antibodies [1], polymeric micelles [2,3], nanosheets [4], focused ultrasound [5], and amphiphatic peptides [6]. Many articles over the years have shown that nanoparticle-based drug delivery systems are promising in reducing tumor sizes in xenograft mouse models. There are a few things that we should take time to ponder on this. First, most formulations seemingly effective in mice have not shown to work in humans. Temperature-sensitive liposomes and ligand-targeted anticancer drugs have failed in clinical studies. To date there are 1996 clinical studies examining the usefulness of gene therapy, and only 2 of them are in the Phase 4 study [7]. Difficulties in successful translation from mice to humans indicate that it is time to rethink our current approaches.

Speaking of treating tumors in the xenograft mouse model, we have to see through the mirage of positive effects in mice. Even in the mouse model, no tumor has been completely eliminated. The mice treated with nanoparticle formulations simply resulted in more shrinkage in tumor size than in the control, and never resulted in complete eradication of the tumor. If a nanoparticle formulation is able to shrink the tumor size after the first administration for a month or two, then one should be able to inject it repeatedly for continued reduction or reaching a plateau of the tumor size, allowing mice to live with cancer. This has not been demonstrated even in the mouse studies. Mice seem to die after a while regardless of repeated injections. It is time to ask the question: Should we continue our current approaches that do not translate successes in mice to humans? Scientists should critically analyze the data and draw conclusions that advance our understanding. Currently, however, data seem to be accepted without critical assessment, if they fit into the biased box of the EPR effect, PEGylation, and receptor overexpression. It is worthwhile to note that many articles published in this journal point out that the presence of the EPR effect is in question even in the mouse model [8], and cancer cells that may have overexpressed receptors do not really increase any drug accumulation [9].

The research done during the last decade can be considered as an evolutionary process, as it produced 'works for now' solutions to a complex set of problems [10]. Simply, further evolution needs to occur for a change from 'works for mouse' to 'works for human'. One may argue that we learned a lot through nanotechnology research that has produced a large number of research articles, even though clinically useful formulations have not been found yet. This, however, is similar to saying that the USA learned a lot through the Iraq War that has produced a large number of counterinsurgency tactics, even though weapons of mass destruction have not been found yet. Scientists may not be able to predict the future, but they should be able to recognize a disturbing

trend, adapt to the new situation, and better prepare for the future through better science. Albert Einstein once said, "We cannot solve our problems with the same thinking we used when we created them". It may not be realistic to expect that the scientists who framed the current box of the EPR effect, PEGylation, and receptor overexpression formulate a new paradigm that can solve the complex problem of tumor-targeted drug delivery. It is time to think in new boxes.

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