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Polymers for drug delivery: the debate continues ▼

The recent perspective article in *Drug Discovery Today* by Hunter and Moghimi [1] successfully brought to the readers' attention the important problems that frequently, if not always, surface during the development of therapeutic synthetic polymers. The article provided a helpful 'wake-up call' to the fact that a better understanding of immunotoxicology, polymer architectural control and polymer degradation is needed.

However, the authors drew several provocative conclusions that were not completely warranted. One conclusion was that immunotoxicological and mechanistic studies of these materials have been neglected. Another was that a major 'paradigm shift' is needed from the current thinking being applied to therapeutic polymers to one incorporating much earlier and more thorough studies on host responses, like immunotoxicological effects, to reduce adverse side effects. Although the authors have rightly raised the issue that more and better efforts in these areas are required, we do not agree that such studies have been neglected, nor that such a paradigm shift is the correct solution to this problem.

The investigation of mechanistic and immunotoxicological aspects of therapeutic polymers, as well as all other classes of novel therapeutics, represents areas where active advancement in the underlying science of biology, molecular genetics, immunology and polymer science is needed, and where active research is ongoing [2,3]. Rather than being neglected, the problem has been, and remains, a continuing need for improved pharmacology and toxicology research.

Perhaps at the heart of the issue is the availability and allocation of resources. Hunter and Moghimis' suggestion, namely a paradigm shift towards the earlier allocation of resources for the investigation of potential adverse effects, would not be the best application of resources. The most appropriate stage to undertake mechanism and toxicology studies, and other aspects that address adverse effects and product development failure, is once therapeutic value, for example efficacy, has clearly been established. The separation of studies in this way is important because a reasonable level of potential therapeutic benefit (i.e. efficacy) is needed to justify building the fuller mechanistic and toxicology understanding. This does not mean that the characterization of candidate therapeutics can not be started at earlier stages, but doing so incurs a higher risk of expenditure of resources on the characterization of agents that prove to be poorly active.

Finally, Hunter and Moghimi drew the readers' attention to specific problems that have arisen in therapeutic polymer development. The problems described have occurred in two different applications of polymers in therapeutics: in one application, they are used as excipients or formulation components, and in the other, they are pharmacologically active agents, for example, the drug substances. The two pose different requirements and, in most instances, different potential concerns about unwanted properties, and yet they are not discriminated in the review. The extent to which the therapeutic window of pharmaceutical products is limited by polymer formulation components must be considered separately from polymeric drug substances.

We applaud the authors for raising these issues. Also, we share their vision that more success will be achieved in the use of polymer systems in therapeutic products, but that more effort and resources are needed in these areas of research. However, by applying resources too early, the game does share elements of Russian roulette because most of the chambers are empty.

References

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