Guest Editorial

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The interaction between nanoparticles and biological barriers

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Biological barriers are truly one of the most perfect biological machines to have been studied. They perform a primary function of preventing undesired access to sensitive organs, while allowing for limited and selected passage across. They thereby manage access of a variety of molecules and assemblies with an efficiency and fidelity that no man-made engineered filter or barrier can even approach. Without such a barrier, for example the lungs, our bloodstream and subsequently all our organs would be exposed to a multitude of dangerous inhalation scenarios. Most delicate of all, the brain would be unable to function in the face of a variety of infections and other challenges.

The basis of the success of the biological barrier is that the primary component of the barrier is composed of an array of tightly joined cells backed up by an array of other cells involved in clearance, immunity and other processes. Thus, while some very small molecular weight molecules can diffuse or passively partition across the barriers, most molecules and other undesirable larger assemblies are excluded, or removed, by active biological processes. Those larger molecules that pass the barrier must traffic across using active energy dependent biological processes, during which they are exposed to many intracellular checks and analyses.

Naturally, the very success of biological barriers in excluding passage can present very significant (arguably, currently often insuperable) challenges for the delivery of therapies across the barriers. For example, many of the more intractable human brain-related diseases ranging from neurodegeneration, persistent drug cocktail resistant viral infection (HIV for example), and glioblastomas, are exacerbated by the difficulty of gaining therapeutic access to the brain. Great inconvenience and expense is added to numerous other therapeutic scenarios in which biological barriers have to be crossed before drugs can act.

Nanomedicine, were it to allow us to address these challenges, would by this achievement alone change the face of medicine, and justify the endeavour. However, a survey of recent efforts suggests that nanoparticles, while they offer important developmental directions, do not automatically, and, naively applied, will not lead to immediate simplistic solutions, based on size alone. Certainly nanoparticles are exceptional in that, due to their size, associated biological interactions follow closely the endogenous biological mechanisms, and transport processes (1). This should make it possible to harness endogenous barrier crossing processes. On the other hand, nanoparticles are also subjected to all the same biological barrier processes that prevent undesirable barrier crossing. Our current view is that, likely, the implementation of a useful targeted nanoparticle strategy will not result from ad hoc approaches and investigations, but require in-depth understanding, and exploitation, of the mechanisms of barrier crossing. All of this suggests a concerted effort is required, spanning nanoparticle design, synthesis, characterization, exposure to relevant barrier models, and mechanistic studies of the outcomes, for any real progress to result. In this edition we gather together several publications to illustrate how this might be achieved.

There are significant specific practical and strategic difficulties that should be stressed, if we are to succeed, in the medium term. While there is no doubt that in vivo studies, and indeed ultimately human studies, will be required to understand and verify key hypotheses, it is likely that key mechanistic understanding of barrier crossing itself will derive from simpler cell level models (2). A major challenge is that few biological barrier models have been deeply studied in the context of nanoparticle interactions, and we have no assurance that any of them faithfully represent the important barrier trafficking processes. Furthermore, the usual means of studying these cell level models, such as cell and trans-well supports, measurement and imaging techniques, whatever their successes for small molecules were, have clear limitations when uncritically extended to nanoparticle-biological barrier studies (3, 4). One may even doubt whether current nanoparticle synthetic approaches will be adequate to engineer a relatively homogenous targeting nanoparticle ensemble with the desired nanoparticle-ligand structure that can continue to function when exposed to real biological media (5).

Given that we may expect the success in finding a nanoparticle resolution to the biological barrier question to be a distance run, rather than a sprint, there are also broader challenges to be faced. Enormous knowledge has been built up over many decades within different biological, biomedical, and clinical communities on the nature and function of various biological barriers (6, 7). More than a generation of research has yielded growing insights into the challenges. The fact that many of the studies did not lead to success in delivery of molecular or, indeed, nanoparticle drugs across the barriers does not diminish the value of high quality research. It will be important to ensure that those with skills in nanomedicine are correctly aligned with that wealth of expertise, whether in academic research, or industry.

Furthermore, the very nature of the challenge means that long-term dedicated research efforts need to be made, sustained, and championed. This will require ongoing and wisely chosen investments. However, some of the finest scholarship in this arena has been pioneered by our seniors during a lifetime of careful and thoughtful work, often without the immediate fruits of success. Indeed, failure has often generated as much insight, as would limited success, but is not so regularly reported in the literature. We will need to ensure that the generation that pioneered some of these ideas can preserve their knowledge and insights and pass them on, ultimately to a new generation of young scientists. Possibly more examples of focussed collections of papers and thoughtful and critical reflections from those that have most experience, combined with well-considered collaborations between more and less experienced researchers, will achieve much.

Few that have thought about this whole arena doubt that nanomedicine has the chance, possibly the leading opportunity, to bring about durable advances in the understanding of biological barriers and in therapeutic applications. Recognition now that the challenge is great, but the prize immeasurable will promote and prepare a new generation for success.

In this spirit, the present special issue contains a set of reviews on select topics related to nanomedical approaches at biological barriers.

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