Journal of Controlled Release 164 (2012) 115–124

Contents lists available at SciVerse ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

"Targeting" nanoparticles: The constraints of physical laws and physical barriers

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ARTICLE INFO

Article history:
Received 1 February 2012
Accepted 13 March 2012
Available online 30 March 2012

Keywords:
Nanoparticles
Targeting
Tumors
Diffusion
Aggregation
Jamming

ABSTRACT

In comparison to the complexities of the body, its organs, its normal and aberrant cells, many nanoparticles will appear to be relatively simple objects. This view is deceptive because the physicochemical properties of nanosystems, although quite well understood on the basis of material science, surface science and colloid theory, are far from simple in practice. While their properties are largely controllable *in vitro*, often purportedly "designed", their administration by any route changing environments conspires to produce additional layers of complexity. Some of the key physical laws and physicochemical parameters governing the fate of nanoparticles on their journey from point of intravenous administration to desired destinations such as tumors are discussed. Much of the science relevant to nanocarrier based targeting has been elaborated in studying purely physical phenomena, but there can be found therein many analogies with biological systems. These include factors that impede quantitative targeting: diffusion in complex media, aggregation and flocculation, hindered behavior of particles in confined spaces, jamming and dispersion in flow. All of these have the ability to influence fate and destination. Most of the critical processes are particle size dependent but not always linearly so. Virtually all processes *in vivo* involve an element of probability. Particle size and properties can be controlled to a large extent, but stochastic processes cannot by definition. Progress has been made, but the quantitative delivery of a nanocarrier to defined sites in tumors is neither inevitable nor yet predictable.

1. Introduction

Great progress has been made in the last few decades in modifying the properties of nanoparticles and their surfaces in attempts to control their behavior *in vivo* [1–3]. Improved control is essential to reduce the often neglected randomness of behavior experienced on administration of drug carrier nanoparticles to the body. Evidence of success in achieving delivery exclusively to specific cell types or organs could be regarded as slender over the period that pharmaceutical nanotechnology has been studied. It is more than 40 years since Peter Speiser and his colleagues at ETH in Zurich introduced the concept of pharmaceutical nanoparticles, as described by Jorg Kreuter, one of the researchers involved [4]. Yet much is promised with the concept of "designer" nanoparticles [5]. Adsorbed or covalently attached ligands of a variety of structures, types and specificity have been used to decorate particles in the hope that this will lead to enhanced effects. First, a hydrophilic corona can reduce the extent of opsonisation and consequent uptake by the Kupffer cells of the liver, as determined in 1986 by Illum, Hunnyball and Davis [6]. Second, and as vital, is the hope that in deploying specific surface ligands interactions with specific and often distant targets will be enhanced. As particle size is a key criterion in nanoparticle technology, maintaining particle size *in vivo* is crucial. The aims of increased colloid stability to avoid aggregation and flocculation on the one hand and decoration of surfaces with specific ligands on the other may, however, have contradictory effects. Long polyoxyethylene chains, for example, will reduce adsorption of opsonins but also usefully enhance steric and enthalpic repulsion between the particles themselves, but also with some target surfaces. One example is that adsorption of poloxmers on nanoparticles prevents their uptake by the gut until they desorb [7]. One is thus faced with the problem of increasingly complex particles being presented to an already complex and changing biological environment as they move from their point of administration to their point of action. The completion of this transport process is, contrary to popular mantra, neither inevitable nor yet predictable *a priori*.

The notion of "targeting" is to an extent a misnomer as particle interactions with receptors are in effect stochastic as are many other processes involved in the transit of particles; extravasation, essential if there is to be closer contact between carrier and target and delivery of active, is a statistical event. Of course the recirculation of carriers, which avoidance of the RES allows, enhances the *probability* of their uptake. But the forces of interaction between particles and receptors can be felt only at short – nanometer – range. They can act only after the particles by chance encounter the attractive force field. Outcomes can be further compromised by the fact that active therapeutic agents carried by most nanosystems can escape during particle circulation, leading to a mismatch between the fate of the drug and the fate of the particle. Perversely the active agent (drug or other entity) may not be

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doi:10.1016/j.jconrel.2012.03.022

released at a sufficient rate for therapeutic activity or might not even be completely released at the site of action. Loading levels of drug in each carrier are key. If 10% of a dose of nanocarriers accumulates in the tumor site, and the drug loading level is 50%, effective delivery is reduced to 5%; should only 50% of the drug be released, this further reduces the available drug to 2.5%. We have of course yet to construe what rate of drug release and local kinetics are therapeutically optimal to kill the range of tumor cells for any of the gamut of cytotoxic agents available today. This suggests that platforms may have to be designed for each target and each drug. There is a valid debate about what is meant by tumor targeting, which it is argued we must define more precisely to separate the concepts of tumor *accumulation* and cellular *uptake* [8,9]. Some imaging techniques may not distinguish between the two as they may detect or measure drug in the vicinity of tumors rather than drug that is poised to be potentially active.

1.1. Scope

In pointing out the complexities of targeting we in no way deny that the research enterprise is a worthy and pressing one. The knowledge gained by using nanosystems as probes of the biological environment has increased the sum of knowledge. The intention of this paper is to invite confrontation of the challenges, which are far from being purely biological. Problems cannot and should not be minimized.

This account reflects on the physical chemistry and physical barriers to ensuring greater success in drug targeting by way of engineered nanosystems. While great emphasis has been placed on 'biological' solutions (with surface ligands) there has been relatively little integrated attention given to the physical issues, such as the effect of surface ligands on the colloidal properties of the particles, although many authors have highlighted the complications involved and suggested ways forward [10–17]. Kostarelos et al. [18] tackle the many issues in the use of carbon nanotubes which can behave quite differently from spherical systems in physicochemical terms. Yet it seems that there is a need to emphasize the limitations of present approaches, as can be seen below.

Nanoparticulates behave in virtually all respects unlike free drugs in solution; physical laws cannot be circumvented or neglected but must be taken into account in nanosystem design. Physical barriers (such as the blood–brain barrier) can sometime be breached but at the risk of adverse events. There are often conflicting issues to resolve, among which is that the reduction of particle size to maximize diffusion, uptake and translocation increases the overall particle surface area and may create problems of physical stability. We must be honest in the appraisal of our science and not overplay or generalize about these complex systems, which have much unrealized potential.

2. Simplifications

The physical barriers that can prevent or reduce the access of nanoparticles to targets such as tumors have been emphasized in many publications, yet an aura of hyperbole surrounds the field of therapeutic drug targeting with nanosystems. This has been detected by astute observers such as Vinck [19], who remarks that nanotechnologists are sometimes guilty of exaggerating the promise of their work. One hundred years ago Wassermann (as recorded in *Nature*, January 1912 [20]) reported the possibility of a remedy for cancer, using the dye eosin to form a "carrier" complex with the active selenium. He employed great caution in the description of his work, emphasizing the fact that it was an experimental cancer in experimental animals and that no clinical application had been attempted [21]. Perhaps we have not as a community learned from Wasserman. Over-simplifications still occur, not only in press-releases, but also in specialist journals. In a discussion of a paper by Lui et al. [22] on the fate in mice of carbon nanotubes – labeled but drug free – in which tumor accumulation reached at most 6% of the dose, it was possible to read [23]: "single walled carbon nanotubes can now effectively target tumors in mice which suggests that nanotubes could form the basis of a safe drug delivery system for cancer therapy," while admitting that loading of a drug, enhanced targeting and optimum release were still issues. In another such commentary [24] it has been stated that the "nanocarriers work by bringing drugs directly to diseased areas of the body, thereby minimizing the exposure of healthy tissues while increasing the accumulation of the drug in the tumor ….. To convert a carbon nanotube into a nanocarrier, it must be able to target tumors, and this ability could be introduced by attaching a peptide or an antibody to its outer surface — an approach already widely used in nanomedicine". Even in 2007 this was surely naïve.

The issue of complexity has to be tackled or "deconvoluted" in the case of cancer [25] even if, as Trabesinger [26] suggests, a formal definition of complexity is not easy to come by. One can apply reductionist approaches to understand components of the process of nanoparticle transport fate, which we have argued [27] is in a way essential if we are to appreciate the whole, but it has been asserted recently [28] that reductionism as a paradigm is "expired" and complexity as a field is "tired". While a sensible reductionist approach may not be able to predict emergent properties, where physical rules are inviolate we may nevertheless be able to predict trends in terms of the parameters that we can alter.

Much effort has been spent on *in vitro* cell studies to demonstrate the specificity of binding of decorated particles with tumor cell types, but these dynamically simple environments have tended to provide false promise [29] in terms of translation to man. Not only are the cells often free in suspension and thus more accessible to carrier and drug than in reality, tissue culture experiments have been found to be dependent on physical properties such as the sedimentation rate and diffusion of nanoparticles [30]. There are many issues to be resolved, not least the reliance not only on tissue culture, but also on small animals in which the issue of scale looms [31]; at a naïve level it would seem that the distance nanosystems must travel in man must exceed that in mice and that this fact alone will cause there to be differences in behavior. Extrapolation of results obtained in small animals to the conduct of nanosystems in human subjects is outside the scope of this paper.

3. Physical laws and barriers

This paper mainly discusses the physicochemical or physical–biological barriers which have led to the lack of quantitative targeting [32], by which is meant delivering a greater percentage of the dose of drug than the amount found in other organs. Related topics to be treated briefly will include *inter alia*:

- Diffusion and Brownian motion in complex tissues including the cell cytoplasm [33] and in the extracellular space [34] in which obstruction effects and binding–diffusion takes place, limiting the translocation of particles;
- Particle aggregation and flocculation *in vivo* adversely affecting particle behavior and not least size — effect paradigms [35,36];
- Particle flow and shear forces and interactions with target (and non-target) tissues and tumor receptors;
- Particles and the enhanced permeability and retention (EPR) effect [37]: size, shape, jamming and kinetics; and
- The intrinsically heterogeneous distribution of both free drug and nanoparticles in tumor tissue and the difficulty in estimating "micro" PK/PD parameters, the kinetics of drug distribution in individual target tumors.