Editorial

Nanotechnologies for site specific drug delivery: Changing the narrative

ABSTRACT

This account of issues in the field of nanotechnologies for specific drug delivery is concerned mainly with its diverse literature. It is a prelude to proposing guidelines to ensure that papers are written acknowledging first the complexity of the task, and second that as there is no such thing as a generic nanoparticle, nor a typical drug, nor standard targets, generalisations are rarely possible. The objective is to discuss some trends which have led to over-confident extrapolations of experimental work in animals to treatment. It is argued that a greater appreciation of the physics, biology and pharmaceutics involved could clarify the sense of any work done and the manner in which this is conveyed in publications. The essential content to be addressed in publications is outlined.

1. Background

Feynman in the Character of Physical Law (1965) wrote “if science is to progress what we need is the ability to experiment, honesty in reporting results – without someone saying what they would like the results to have been – and finally – an important thing – the intelligence to interpret the results without preconceptions.”

More than half a century later we need to rehearse these sentiments in discussions of nanotechnology for site specific delivery. Our interest in this stems not least from the fact that in 2004 the International Journal of Pharmaceutics introduced a section for papers on pharmaceutical nanotechnology. Today around one third of submissions fall into this category. Given the passage of time it is appropriate to assess to what extent the promise of nanoparticle site specific delivery has been fulfilled. Here we concentrate on delivery to tumours, acknowledging that there are many other targets. Those working in the field must ensure that publications are as open, accurate and frank as they can be, and that conclusions are justified by the actual work done. Many have felt for some time that the literature of “targeting” nanotechnology has exhibited a tendency to over-optimistically extrapolate its significance. Work has almost exclusively been conducted ex vivo or in vivo in small animals. Such studies, while of value, cannot be held to be a prognostic signal of therapeutic success (Crommelin and Florence, 2013). Much of the literature in the field is skewed towards the positive. The most cited papers in the field are those that are positive in outlook. One might include the review by Peer and colleagues (Peer et al., 2007) which has attracted to date some 5500 citations. Papers which emphasise complications in our endeavours seem less attractive to cite. One rarely sees negative or “disappointing” results published. Disappointments, of course, may be a result of mistaken preconceptions, stemming from an underestimation of the complexity of the systems we deal with. Even ex vivo work can be difficult both to interpret in terms of the behaviour of different nanoparticles and to estimate the significance of the systems to in vivo conditions.

Nanoparticles are injected into a dynamic and changing environment. Often seen statements such as “nanoparticles target tumours” are too glib and indeed misleading. There are terminological issues too. “Targeting” cannot be the correct description of an effect that exists only at the end stage of a tortuous particle trajectory from administration to within nanometers of an actual target element? And we must ask “which nanoparticle, which tumour, which model, which animal, which drug at which dose? The concept of dose is key, as the drug content of nanosystems is not a dose in any sense. So reflection suggests that a more correct general statement is that “some nanoparticles can accumulate to a low degree in some target sites.” Wilhelm et al. (2006) have provided the basis for such sentiments, having analysed ten years’ of publications on nanoparticle delivery to tumours enabling them to conclude that “only 0.7% (median) of the administered nanoparticle dose is found to be delivered to a solid tumour.” Naturally this implies a check on ambitions to use existing systems in human studies. Targeting strategies raise the bar somewhat but not significantly.

This is far from saying that the research conducted so far is not of value. Indeed the role of academic research is to advance knowledge and understanding, not primarily to produce therapeutic products. After all astrophysicists do not produce stars, they only find them and try to understand them.

1.1. Myths and fictions

The sociologist Maaestrutti (2011) in her book “Imaginaires des nanotechnologies: mythes et fictions de l’infiniment petit”1 deals with the broader topic of nanotechnology in its many guises, but many of her views on myths and fictions apply perfectly to the area of the much vaunted descriptors “direction, propulsion, guidance” or “targeting” of nanosystems to tumours and other tissues. In brief Maaestrutti’s narrative is about the gap between what is promised and what research actually shows. Our collective imaginings and not least the artistic representations of nanosystems and their behaviour in biological environments may be beguiling, but cannot address the dynamic and
stochastic realities, the exquisite complexity of bifurcated capillary beds or the dynamics of blood and particle flow at junctions. It is easier to illustrate nanoparticle targeting than to achieve it. The probability (not the foregone conclusion) of many particle-cell interactions in vivo, and the role of chance need greater attention and understanding. Extravasation leading to tumour access is a process with very low probability for each nanoparticle on each circulation in the blood.

1.2. Facts and failings

Maity and Stepecsny (2015) have confirmed some aspects of problems in the literature. In their analysis of 77 papers describing research on nanoparticle drug delivery and targeting to intracellular organelles they found, remarkably, instances of failure even to characterise fully the nanosystems used. There were instances where there was a failure to quantify accumulation, less than a quarter of these papers presenting quantitative data on target access. Sixty-five percent of the papers describe particles with ligand-decorated surfaces, but the majority of these papers failed to quantify the efficacy of such embellishments. From an editorial perspective we must agree with Maity and Stepecsny in their conclusion that “insufficient efforts are devoted to quantitative analysis of … major formulation parameters”. It is incredible in a field so fundamentally dependent on the size and nature of drug carriers, that some do not properly define particle (or construct) diameters, nor seem to recognise that all the factors that control the physical stability and thus the effective particle size of colloids apply to nanoparticles. A nanoparticle suspension dispersed in water buffered to a physiological pH is a poor predictor of sedimentation, aggregation and adhesion even in cell culture systems, let alone in vivo, where the flow and shear forces in blood may be vital in determining progression. Is this inadvertent neglect of what is known? Or can it be a simple lack of knowledge of what is relevant?

1.3. Retrieving basic knowledge

There can be no disputing that the application of pharmaceutical nanotechnology to achieve precision in the delivery of active molecules to target organs and sites is a hugely complex and challenging area of research. Indeed one challenge is to admit that in targeting tumours we have not reached an essential baseline, as the analyses of Wilhelm et al. (2006) show. If the majority of papers cited are those which are optimistic and positive the field is biased. Often a blind eye is cast on the influence of complex interactions of chemistry, physics and biology. Complete textbooks are devoted to key aspects of science that underpin particle behaviour in different settings. To cite some on my shelves there are treatises on the physical biochemistry of biological interfaces (Baszkin and Norde, 2000), van der Waals forces (Parsegian, 2006), colloid science (Hunter, 1989), cohesion (Rowlinson, 2002) and biomechanics (Fung, 1993). If these or equivalent texts are not pored over then the true appreciation of the complex behaviour of nanosystems both in vitro and in vivo will be not be uppermost in the minds of researchers.

Nanotechnology is a relatively new term but it has its antecedents in colloid science certain from the father of colloid chemistry Thomas Graham’s time in the 19th century. Some forget the lessons of the past, or have not kept in touch with them leading to what Arbesman (2012) calls the half-life of acquired knowledge. Hence older textbooks may need dusting down and rereading. In the introduction to the Physical Chemistry of Cells and Tissues, Hober (1945) described the subject as “physiology as a branch of physical science dealing with life as a physical, though exceedingly complex system, that may be subjected to scientific analysis”. An even older textbook is titled Dynamical Therapeutics. (Webster, 1898) which indeed could be an alternative definition of nanoparticle targeting. The physics and chemistry we know has to be translated into dynamic situations involving many elements of probability at critical points on nanoparticles’ indirect trajectory.

1.4. Questions of definition

There are also some basic issues in our precisions, caveats and definitions and questions of the use of simplified terminology:

- First there can be no single or simple definition of “a nanoparticle” as even the defining feature of size is insufficient in systems with diverse morphologies, shape, degrees of flexibility, material nature, chemical interactivity, surface decoration, flow properties or their tendency to aggregate. There are also differences in the probability of extravasation and interactions with critical sites, wherever these are located within the target domain.
- Second there can be no simple definition of a “tumour” either in terms of its cellular and genetic nature or morphology. There is the compounding factor of the physical and biological change in tumours as they grow and respond to certain stimuli. Any predictive theory of the fate of administered nanoparticles requires measures of all the indices mentioned above, and more. Some individual events or processes are affected by what has gone before.
- Third: the active agents we wish to deliver have themselves different physical and chemical properties and also modes of action and intrinsic efficacy; some might indeed interact with the material of the nanoparticle in a manner which might affect its release and activity.
- Fourth: if experiments have been conducted in animals then extrapolation of results to the human condition is a step too far. Linguistically, ethically or scientifically results from such studies cannot be morphed into “treatments.”

1.5. Taking stock

In the cold light of day it is vital that we take stock of where we are. This is not a recent necessity: we cannot have been blind to the complexity involved in the trajectories and barriers encountered by drug laden and surface decorated nanoparticles. To face up to the facts is not to decry objectives. We can be optimistic, but with moderation. Jeong et al. (2010) in the title of their paper have ambitions to challenge “nature’s monopoly on the creation of well-defined nanoparticles.” Nature has taken eons to evolve exquisite particles such as low density lipoproteins and viruses. In comparison the nanotechnology field has had a nanoscopic timetable.

Au et al. (2016) describe the relevant “determinants, barriers, challenges and opportunities” in this ambition, interrogating as many 40 critical parameters in the delivery by carriers of drugs to extra-cellular and intracellular targets. Time indeed for reflection. Time to think of the wider issues, and in particular of analogous models of the processes involved in drug delivery and targeting in cognate or even seemingly disparate fields. We can continue to construct nanosystems with special surface properties and administer them to animal models and in this way slowly gain knowledge of what is effective and what is not, but our claims of effectiveness have to be better defined. Theoretical analyses are perhaps a better starting point so that experiment can test theory rather than hope.

There have been two recent reflections (Park, 2017; Leroux, 2018) which discuss some aspects of the syndrome: the conflicting attractiveness of “novelty” and “breakthroughs” and the inconvenient truths about the field. Klein (2011) refers to the “nano” prefix being a requisite for obtaining the necessary credits for research. What else explains the fact that microemulsions (which have diameters of 1–100 nm and have been known as such since 1954 after their discovery 11 years earlier by Hoar and Schulman (1943)) have now transmuted into nanoemulsions? There is too the re-titling of micelles as nanomicelles (Wen et al., 2011), and liposomes as lecithin nanovesicles (Al-Remawi et al., 2016). Those like myself who were studying micellar surfactant systems in the 1960’s or studying 1–5 nm thick soap films under the tutelage of Karol Mysels (Mysels et al., 1959) were either precocious nanotechnologists, or just simple Angstromologists. There is thus the
concern that pharmaceutical nanotechnology is inflating its domain and success by retrospectively claiming systems such as liposomes and albumin-drug complexes as nanotechnology’s clinical successes. The naming of nanoparticulate systems should be the subject of some international agreement and controls, otherwise the literature will become even more difficult to dissect and digest. Novelty does not extend to inventing new descriptors for long-established systems.

1.6. Inflated interpretation in drug delivery

The problem of expressed over-expectation does not exist solely in nanotechnology. Caulfield et al. (2016) comment on “stem cell hype.” Oral insulin “therapy” is implicated too: one has asked if it is indeed a chimera (Florence, 2017). Why do we not object to comments (Anon, 2018) on a paper bereft of animal studies that “according to the results the optimized nanoparticles can be used as a new insulin oral delivery system.” Scientists need not only to have the perspective but also the humility to describe outcomes as modest at times. They must edit press releases. Items such as “nanoparticles deliver anticancer cluster bombs” do not serve well the authors of the work involved; nor does the description of another as an “extremely selective and lethal cancer treatment” relating to a paper based on animal studies. This goes on to suggest that “this new treatment could mean improved survival rates for roughly 6,000 US women….” We have been criticized in the past for writing modestly about facing up to complex realities (Ruenraroengsak et al., 2010) in the quest for specific or targeted drug delivery especially and not only to tumours. The complex realities are not those of our nanosystems, although as Leroux (2018) rightly suggests, complex nanoparticles simply complicate the prediction and interpretation of their in vivo behaviour.

1.7. Experiment, computation, theory: an interdependent trio

There are three modes of investigation: experimental, computational and theoretical (Goldenfeld and Kadanoff, 1999). There exist many experimental studies in a variety of model systems, with different drugs and different tumour models, indeed an impossible amount to read, to analyse and to digest

1. There is now sorely needed a more thorough theoretical grounding to the field. The probability of particular event such as the much vaunted process of nanoparticle extravasation, particle transport and subsequent arrival at target sites and the activity of the biologically active agent if and when released from the delivery system must be a precursor of further experimental efforts. The essential pairing of particokinetics and pharmacokinetics (Teegarden et al., 2007; Zhu et al., 2013) or indeed spatiokinetics (Au et al., 2016) in tumor environments need to be better understood. There is not the luxury of a single clear scenario to predict the fate of nano-systems (Al-Jamal, 2013).

1.8. Recognising realities from simpler systems

Even the simplest physical systems which can be studied with great precision involve multiple parameters. A paper on the sedimentation of small particles by Guazzelli (2006) has a sub-title expressing the sentiment: How can such a simple problem be so difficult? Many “simple” systems studies in controlled conditions are indeed complex. So why indeed should we assume that nanoparticle targeting in vivo is anything but complex? The capillary wicking of water in sponges (Ha et al., 2018) may be imagined to be related to some processes that are involved in the late-stage access of nanosystems to tumours. Be that as it may, the controlled structure, the simple nature of the penetrating medium and the precise ability to measure the process nevertheless gives rise to an explanatory equation of the wicking velocity having nine physical constants, namely the liquid-air surface tension coefficient, liquid density, gravitational acceleration, the radii of macro- and micro-voids, driving pressure, radius of curvatures of the front meniscus, permeability and the hygrosopic strain of the saturated sponge.

There are intriguing particle behaviours still being discovered. One might see as Shimokawa and Ohta (2011) observed a new fractal pattern of particles derived from soluble coffee poured into a layer of milk. The complex patterns form spontaneously. Under certain conditions nanorods may form rings (Khanal and Zubarev, 2007). There is no need to underestimate the complexity of particle behaviour in vivo when it is multiplied by the number of challenges and changes of environment they experience en route to their targets, and not least those caused by the nature of tumours which change with time. We need to address these issues, not bury them by reciting the enhanced permeation and retention (EPR) effect and similar shibboleths without pondering on the physics, biology and chance involved in allowing access to and accumulation in targets. This is not a forgone conclusion for all nanoparticles, nor under all conditions (Nichols and Bae, 2014; Maeda, 2015) as we have discussed.

1.9. The distant territory of tumours

What precedes access to the tumour region? Extravasation is dependent on the attachment or not of particles to red blood cells (Pan et al., 2018) and affects their deformability; escape is also dependent on the geographical location of nanoparticles having traversed multiple bifurcations in capillary vessels, where of course nanoparticles do not follow identical trajectories. Advection and diffusion are reduced with the increasing complexity of the microvasculature as Mascheroni and Penta (2017) point out, thus bulk flow and access to specific sites is diminished. Once drug is released from the carrier particles (a variable process dependant on particle, drug and site of deposition) it must diffuse into the target cells. Formulation additives such as surfactants can enhance the penetration of free drug in tumours, but such additives in the particles themselves might also aid premature release of the drug en route to the target. Theoretical calculations of drug penetration depth in solid tumours (Namazi et al., 2016) of the order of 20–150 μm, are valuable in giving dimensions to ambitions. Different drugs, as expected, penetrate to different extents, varying by a factor of around 8 fold. The values obtained agree closely with experimental data. Results for doxorubicin illustrated a two-fold effect of formulation.

1.10. Expanding the narrative of the discipline

Perhaps one of the issues we are addressing here is the language we use in our papers and at conferences. We must incorporate into what we say and write the phrases, the knowledge we learn from cognate disciplines. These would alert us to concepts which might include the discovery of slowness (Guigas and Weiss, 2007), the dynamic personalities of proteins (Henzler-Wildman and Kern, 2007), the history-dependent dynamics, random walkers in confinement (Guérin et al., 2016) or the chaotic dynamics of jamming (Banigen et al., 2013). Other notions that are relevant to nanoparticle transport and essential interactions encompass anomalous local viscoelasticity in actin networks (Amblard et al., 1996), and at their destinations Brownian motion in dire straits (Holcman and Schuss, 2012). Phenomena such as spatial chaos and

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4 Google Scholar interrogated for papers on Nanoparticle targeting to tumours since 2014 reveals ~17,000; from 2018, ~6200 excluding citations. Reading 20 papers a day, 100 per week, 400 per month, would require > 3 years.
5 In an implanted tumour of 5 mm diameter, 100 μm penetration by the drug is equivalent to 0.4% of the tumour volume, equivalent to that found in some tumour spheroid studies. Timescales are of course important.
complexity in the intracellular space of cancer and normal cells (Pham and Ichikawa, 2013) are all part of the narrative. There are also relevant phenomena such as hydrodynamic memory in Brownian motion (Franosch et al., 2011), mobility of axisymmetric particles near elastic surfaces (Daddi-Moussa-Ider and Gekle, 2016) and Brownian behaviour in a random array of particles (Franosch et al., 2010). There is also the issue of the effect of the aspect ratio of particles in tumour tissues (Chariou et al., 2016). Too often the field has appeared as if success was pre-ordained and we are surprised by, and unprepared for, failure. To modify the phrase of Grizzi and Chiriva-Internati (2006) – we hope for simplicity and misunderstanding complexity! We should expect complexity because that is the nature of the beast, be it mouse, rat or man, or nanoparticle.

2. Essential elements of papers for submission.

The many aspects of the delivery of nanoparticles to specific sites and the literature’s attention to this have been discussed. Guidelines for the content of papers must have items specifically addressing the points so far made.

2.1. Evidence of quality control and assurance

Quality control and quality assurance are essential elements in the production of high quality medicines. How often are quality control procedures applied to the nascent nanoparticle systems in our laboratories? In an article in Nature, aptly entitled “Quality Time,” Baker (2016a) argues that while it is not glamorous or exciting, quality assurance is a necessary part of the scientific endeavour. It applies to the provenance, purity and stability of drug substances and all reagents used, to polymers, surfactants and also to the correct functioning of equipment. Drug samples purchased from some sources may not be what they claim. For example, eighteen independent suppliers of the kinase inhibitor bosutinib have been found to be supplying not the molecule itself but an isomer. Analytical assessment of 600 samples of kinase inhibitor bosutinib have been found to be supplying not the molecule itself but an isomer. Analytical assessment of 600 samples

2.2. Evidence of reproducibility

How many papers demonstrate that their results are reproducible, not through the use of aliquots from single samples but through repetition of work ab initio? The scale of the problem of irreproducible data in published papers is being revealed. Having myself spent half of my first post-doctoral fellowship unsuccessfully trying to repeat a published method to prepare monodisperse emulsions, and having no response from the authors about my difficulties,6 I recognise the issue acutely. Tellingly researchers at Amgen reported in 2012 their inability to reproduce the results recorded in 47 of 53 papers chosen as key papers in the field of cancer (Baker, 2016b). A Nature editorial on repetitive flaws (Anon, 2016), points out that the US National Institutes of Health is demanding more care in experimental design, justifying both it and the premise of the work, as well as anticipating potential biological variables.

2.3. Hypothesis testing and reality checks

A paper which is devoted, for example, solely to the encapsulation of a single drug into a polymeric or other material and drug release rates determined in vitro is of incremental importance, even when the system’s interaction with target cells in culture may have been studied. The question is what hypothesis is being examined? Without an understanding of the location and physical state of the active agent within the nanosystem and the significance of both the total drug content and drug release rates in relation to the time the nanoparticles will circulate in the body, little is gained. Many nanosystems lose their drug quickly in burst release in in vitro tests, sometimes as much as 80% in a short time span relative to their potential lifetime in vivo. The arithmetic is stark. If the in vitro dissolution rate measurements have any significance in vivo even if the particles carry an (unusually high) drug payload of 50% w/w, the loss of 80% of the drug early on in its route in vitro leaves only 10% of the encapsulated drug for diffusion towards the target cells, within the target cells and achieving action. If, by the oral route 5% of the particles are absorbed primarily by way of Peyer’s patches (Jani et al., 1989, 1992), only 1% of the drug dose is left for biological action mediated by the construct. This aside, particle samples are rarely mono-sized, hence where size is of crucial importance, each particle will not have an equal uptake or access to targets. Nanoparticle uptake is size dependent. The effect of production and formulation parameters on reproducibility of size must also be investigated. Data should be analysed for what they are, and what they show.

2.4. Enhancing the wider value of publications

All journals have a role to play in ensuring that papers which are published add to verifiable knowledge. They must ensure too that failure is discussed and any consequent changes of direction proposed. We must ask for more information on what many consider to be the routine of any paper, namely the material and methods used, but not only the dry details of suppliers but proof of the quality of drugs, solvents and related materials. Fig. 1 summarises key issues and should serve as a quick guide to essential features to be expected to be discussed in submitted manuscripts.

2.5. Necessary elements of papers on nanosystems for site-specific drug delivery.

There are many lacunae in our knowledge of nanoparticle based targeting and delivery and action. If this is not recognised in papers this is effectively an admission, as Ghaemi (2009) discussed, of problems caused by “the failure to know what isn’t known.” We need more awareness of the proven facts about drug delivery and targeting by nanosystems, as well as what is as yet unknown or not applicable to all systems because of the idiosyncrasies of individual constructs. Crist et al. (2013) which relay the common pitfalls in the field. There

6 My conclusion was that the particle size analysis data by microscopy was selective and thus flawed and that indeed the systems were not mono-disperse. The paper in question was M.A. Nawab and S.G. Mason (1958) The preparation of uniform emulsions by electrical dispersion J. Colloid Sci., 13, 179–187.
is the concern addressed earlier that pharmaceutical nanotechnology is inflating its domain and successful direction by retrospectively claiming small materials, systems and objects as part of it. While it is of course not possible to determine every aspect of systems studied, Table 1 should be considered: it is perhaps alarming, yet it is not complete in every detail. Nevertheless these points should be addressed at least.

2.5.1. Particle size distribution

An essential element, indeed the crux of nanotechnology, is the size of particles and constructs employed to deliver actives. As many systems are not monodisperse, an appropriate particle size distribution must be measured and reported. The need for precision in this regard is emphasised by Gaumet et al. (2008) who recommend the use of at least two particle sizing methods. Electron micrographs of samples must be typical of the batch. Batch to batch variation is a feature that can be determined in part by particle size analysis. As the medium and formulation ingredients can affect many aspects of their colloidal behavior, the mean size and size distribution must be studied, including in vivo: e.g. aggregation, etc.

2.5.2. Particle shape

Many systems such as those based on carbon nanotubes are aspherical. Others may be ellipsoidal, plate-like or indeed possess asperities which affect many aspects of their colloidal behavior in vitro and in vivo, including particle–particle, particle surface interactions, flow and sedimentation. How does one compare a typical dendrimer with a polymeric nanoparticle? Ideally the effect of particle size distribution and shape on the diffusion and interaction of the systems should have been investigated.
2.5.3. Surface properties

It is clear from colloid stability theory that particle surface charge (e.g. zeta potential) is a key factor in stability as well as in cell interactions. Surface charge should be measured under appropriate conditions, for example as a function of pH and electrolytes, as well as in biological fluids and cell culture media where appropriate. The effect of molecules and macromolecules adsorbed or covalently attached on the surface properties of the particles should be examined and reported. Estimates should be made of the components and composition and molecular dimensions of the particle corona by determining inter alia the particle size of native and decorated particles. The stability of the corona should be examined and reported.

2.5.4. Nature of the drug carrier nanoparticles

It is insufficient to report simply the extent of uptake of a drug or other active into a nanosystem without, ideally, investigation of 1) the thermodynamics of the process, 2) the location of the drug and 3) any interaction that may have occurred between the drug and the polymer or other material used to fabricate the system. The homogeneity or spatial distribution of the drug within the particle is likely to be important and should be assessed whenever possible. Is the physical state of the drug amorphous or crystalline? Is there surface adsorption of the drug? Is the system chemically stable? Does the drug react with any other components of the nanoparticle?

2.5.5. In vitro release studies

The release profile of drug from nanoconstructs should be measured in appropriate aqueous solvents. The appropriateness of the profile for continuing the evaluation of the system for in vitro cell studies or animal studies should be argued, especially in relation to the conditions and timespan of the presence of the formulation in cell culture systems or in the blood circulation and thus onward transit to target cells.

2.5.6. Cell lines

The choice of cell lines must be justified in relation to their relevance to the drugs employed and the nature of the ultimate target disease. The provenance of the cultures should be explicitly detailed and their experimental handling fully described. Cell studies should include a discussion of any physical interaction of the nanosystems with the cells, and any effects of components of the formulation on toxic effects examined.

2.5.7. Animal studies

The use of animal models takes research on delivery a step further, but data have to be strictly examined for their relevance, if any, to human studies (Gould et al., 2015) The European Commission Workshop titled “Of mice and men – are mice relevant models for human disease?” is of help in this regard (Report, 2010). Riviere (2013) has discussed in particular whether in vitro to in vivo correlations and interspecies extrapolations realistic. All this is not to deny that the animal studies are valuable, but to ensure that any textual extrapolation are used cautiously. Often missing are the micro-pharmacokinetics at the tumor level as well as standard pharmacokinetic profiles in test animals. Attempts should be made to determine the fate of nanoparticles in the animals in relation to the choice of dose of both drug and nanosystem injected (He et al., 2011).

2.6. Conclusions

- It is insufficient to report the encapsulation of a drug or active molecule in established materials without the issues above having been addressed.
- Nanoparticles that are claimed to have potential as targeting vehicles must be tested in vivo.
- The effect of any treatment which alters the properties of the particles, such as PEGylation or adsorption of surface targeting moieties must be compared with appropriate controls.
- Claims for systems reported must be factual. Extrapolations of initial work and attribution of results to phenomena such as the "EPR effect" or oral uptake are not acceptable without these being specifically considered and examined.
- Targeting and localised drug release must be quantified.
- Papers should not claim that systems studied are “promising for therapy or treatment” as these can only be proved through human clinical studies.
- Abstracts and titles of papers should avoid the use of adjectives such as “novel”, “successful” or “promising.”
- Papers should be written with the readers in mind, that is with style and precision (Florence, 2017).

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Declaration of interests

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