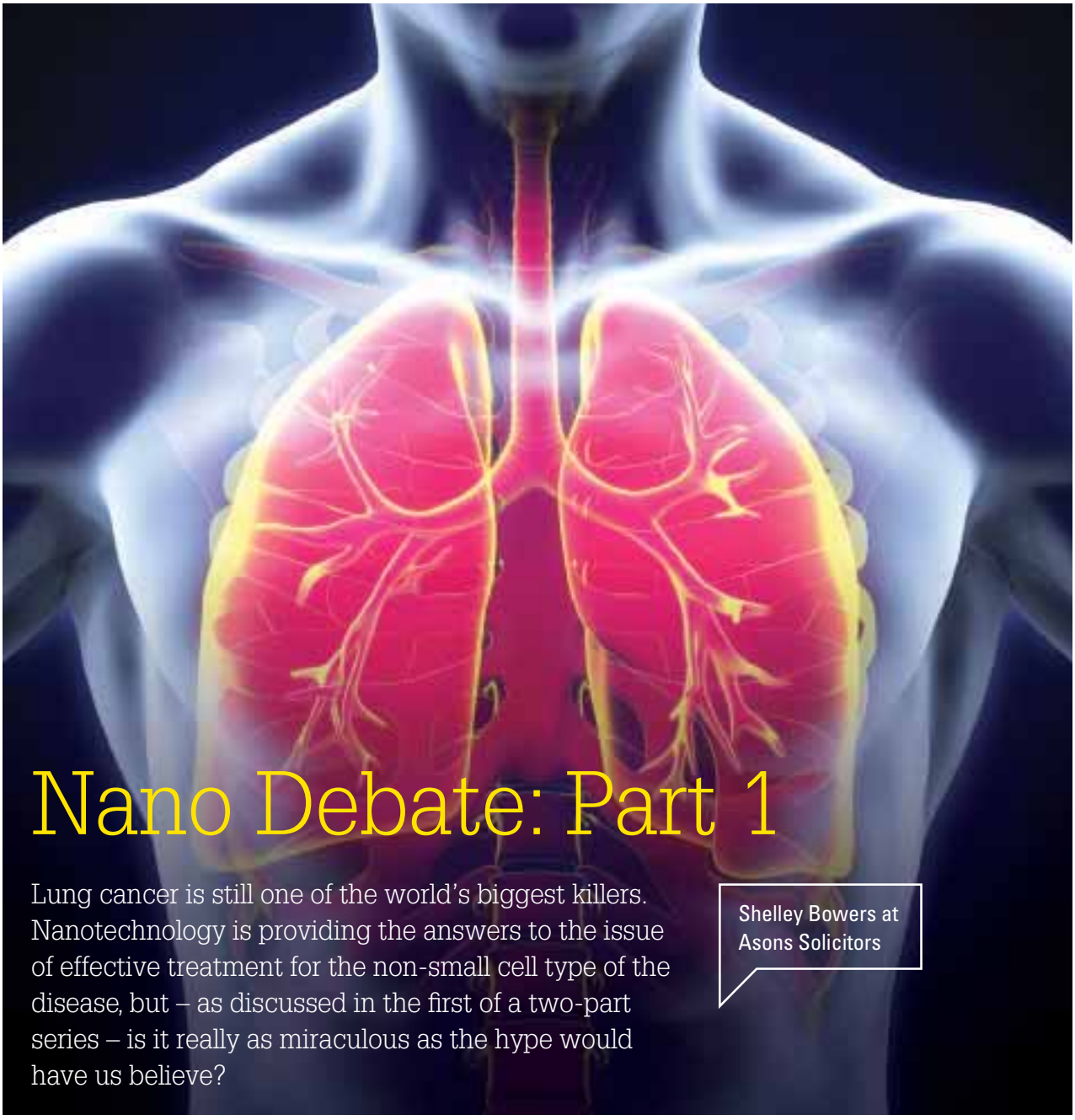

Nano Debate: Part 1

Lung cancer is still one of the world's biggest killers. Nanotechnology is providing the answers to the issue of effective treatment for the non-small cell type of the disease, but – as discussed in the first of a two-part series – is it really as miraculous as the hype would have us believe?

Shelley Bowers at Asons Solicitors

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Lung cancer is lethal. It is the world's number one cancer killer, accounting for over 1.5 million deaths in 2012 (1). Approximately 85-95% of cancer mortality is due to non-small cell lung cancer (NSCLC), with the small cell type accounting for the remainder. There were over 35,184 people diagnosed with lung cancer in the UK in 2012, making it the second most common cancer killer today (1).

A major contribution to this high number – along with the continual lack of accurate, early-detection diagnostic tools – is an inability to find non-toxic, efficacious treatment options. The result of which is an over five-year survival rate of only 7.8% for males and 9.3% for females (1). These are very sobering figures.

Is the Answer Nanotechnology?

Nanomedicine has come on leaps and bounds in the last few years, and the niche world of nanodevices offers a tantalising glimpse into the future of lung cancer treatment.

But, as an emerging area of study, with both triumphs and catastrophies in its recent past, the jury is still out on nanomedicine. While the benefits cannot be disputed, what of the side-effects? Are there any? Do we even know what they might be? And what timeframe do we really need to assess the true long-term risk potential?

This article gives examples of some of the major life-saving benefits of a nanomedicine, focusing on the liposomally encapsulated cisplatin drug, known as Lipoplatin. It also delves into the concerns surrounding this potential new wonder drug that are yet to be resolved.

Side-Effect Reduction

The current first line NSCLC chemotherapy treatment, cisplatin, has terrible and wide-ranging side-effects – including acute nephrotoxicity, which can lead to death (2).

Despite debilitating reactions, it has remained one of the most effective NSCLC treatments since it was first introduced in the 1970s (3). Researchers hope to find ways to reduce its toxicity through the application of targeted delivery nanomedicine. In 2004, researcher Teni Boulikas decided to apply this idea to address the issue of a 20% incidence rate of nephrotoxicity in cisplatin patients.

Cisplatin is rapidly excreted in the urine shortly after being administered. On its way out of the body, its high level of toxicity causes renal tubular dysfunction and impairment of renal function through a process of necrosis and the apoptic death of the kidney tubule cells. Acute renal failure, and even death, can occur after just a single dose (4). This means cisplatin, which needs to be given in high doses to be successful, is dose-limited by its negative effects (5).

To counteract these potentially fatal side-effects, Boulikas has developed a nanomedicine known as Lipoplatin. Lipoplatin liposomes are nanosized vesicles, constructed of bilayered phospholipids. The nanoparticles are composed of lipids and cisplatin, and are no more than 110nm in diameter (6). Cisplatin forms the central core; this is surrounded by a lipid bilayer made up of, among other things, soy and cholesterol. The coating allows the Lipoplatin to move freely in the body, by masquerading as a nutrient for the tumour cell (7).

Treatment Travel

The polyethelyne glycol (PEG) polymer coating added to the nanoparticle enables this highly toxic substance to travel, undetected by the immune system, for long periods. Furthermore, the use of a hydrophilic inert polymer coating allows the particles time to travel to the desired location, whereas non-PEG coated cisplatin is rapidly cleared by macrophages (8).

On arrival at the tumour site, Lipoplatin enters via extravasation (8). The nanoparticle easily permeates the fragile endothelium of the vasculature created during neoangiogensis, and accumulates in the tumour cell mass (4). Lipoplatin levels of up to 200 times higher have been observed in tumour sites, compared to surrounding normal tissue (9).

In comparison, when cisplatin alone is infused into the blood stream, it simply disperses throughout the body – including reaching vital organs – killing healthy cells along the way, and creating the devastating side-effects already outlined. Essentially, the addition of the nanoparticle keeps the toxic effects of the cisplatin away from the healthy cells, ensuring it reaches the areas where it is actually needed (8).

Increased Cell Uptake

At this point, Lipoplatin deploys its final weapon. To aid in tumour cell uptake – and, thus, increase the efficiency of the drug – Lipoplatin nanoparticles are equipped with a fusogenic lipid, dipalmitoylphosphatidylglycerol (10). This helps them fuse with, and breach, the most significant barrier to targeted delivery of cisplatin: the tumour cell membrane (7). Once inside the cytoplasm, Lipoplatin offloads its toxic cargo, destroying the cancer cell (10).

It is this combination of factors that contributes to the lowered nephrotoxicity of Lipoplatin (4). And, given that nephrotoxicity is a major hindrance to the application of cisplatin for NSCLC, the development of Lipoplatin is certainly a step in the right direction.

This reduction in side-effects has an added benefit: it enables treatment to take place in an out-patient setting. When administering cisplatin, a two-day hospital stay is required. Dispensing with this need not only offers an economic benefit for the hospital, but translates into a better quality of life

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for patients (8). This is an important factor, and one which could play a vital role in recovery.

Lipoplatin is just one drug among many. The idea that this is only the tip of the nanomedicine iceberg is both exciting and deserving of detailed investigation. So, what might stand in the way of the large-scale application of nanomedicines?

Unknown Territory

Though there is undoubtedly much we do know about nanomedecine, there is an equal amount yet to be discovered. To begin with, there is a debate over the safety of nanoparticles in the long term. As an emerging technology, there is little to make reference to regarding the adverse or unintended effects of nanomedicine (11), as it was only launched 14 years ago (12).

While some nanomedicine, such as Lipoplatin, has reached successful Phase 3 testing (13), most trials in existence are animal models (11). As is the norm with any new medicine, a period of preclinical trials are carried out on animals, and on cells *in vitro*, before clinical trials on humans can begin (14). This takes time and, so far, research has not gathered enough evidence to give any real indication as to the acute and long-term effects of introducing nanoparticles into the human body.

It is also important to remember that even drugs that have passed Phase 3 trials can still produce unexpected, negative side-effects (15). Take, for example, an experiment carried out on trial volunteers in 2006. Following the obligatory testing on rats – at a dose 500 times that intended for human use (16) – and a period of evidence gathering, researchers switched to testing on humans.

An injection of an experimental drug, known as TGN1412, was given to six healthy male volunteers. Severe headaches and back pain began an hour after administration. This was followed by convulsions and vomiting, a rise in blood pressure and swelling of the head. A brief respite soon deteriorated into organ failure, resulting in extended periods of time in hospital (17).

This brings us to two conclusions. One is that it is not always possible to extrapolate from animal to human models – the animals displayed no adverse effects in this trial, even at 500 times the dose (18) – and the other is that substances that can produce an immune response should be handled very carefully (19).

Despite the correct experimental procedures being followed, the study still ended in near disaster. The reason for this happening was a lack of previous research to draw on. Had this been available, it is likely the outcome would have been different (20).

Standard Procedure

The absence of standardised testing procedures has also raised concerns (17). Currently, *in vivo* testing lacks widely-accepted protocols for the experimental examination of nanoparticle behaviour (20), and early experiments with carbon nanotubes revealed the researchers' lack of detailed knowledge about nanoparticle behaviour in the body.

It was discovered that injecting carbon nanotubes into mice created an effect similar to asbestos (20): cutting and clogging the lungs, creating inflammation, problems with breathing and, possibly, cancer (21). Similar experiments showed that only certain shaped carbon nanotubes created harm. And when further experiments revealed a huge accumulation of nanotubes in the animals' spleens and livers, researchers were shocked – particularly as the mice had been symptom-free for four months. However, subsequent trials failed to reproduce the same findings (20).

Such confusion highlights how little is currently known about this field of medicine. At this early stage in development, it is not possible to know the adverse effects of nanoparticles, or even which ones might be dangerous (17).

What is clear is that nanoparticles remained in the mouse body, in vital organs, for over four months. What then, does this mean for the long-term prognosis? Especially when you consider that a gathering of larger particles can cause cancer via the inflammatory process. It appears highly probable that nanoparticles may have the same inflammatory properties, especially as their nanoscale size allows them to gather in greater numbers (17).

Nanoparticle Behaviour

Another apprehension of nanoparticle use, for lung cancer treatment in particular, is the apparent ability of particles of less than 6nm to pass from the lungs into the bloodstream and out through the kidneys (22). While this may at first appear to be a benefit, it comes loaded with risk from the characteristics given to the nanodevice – for example, a molecular charge. This could damage other cells as it passes through the body.

Adding to this concern is the realisation that nanoparticles display differences in behaviour between *in vitro* and *in vivo* experiments. The reason for this is that nanoparticles are heavily dependent upon their microenvironment, and may change in shape and size once inside a living organism. For example, smaller 1nm particles could congregate together, or a larger 100nm particle could disintegrate into smaller 1nm particles (23).

This clearly presents a number of issues with controlling the migration of particles. But even more worrying is

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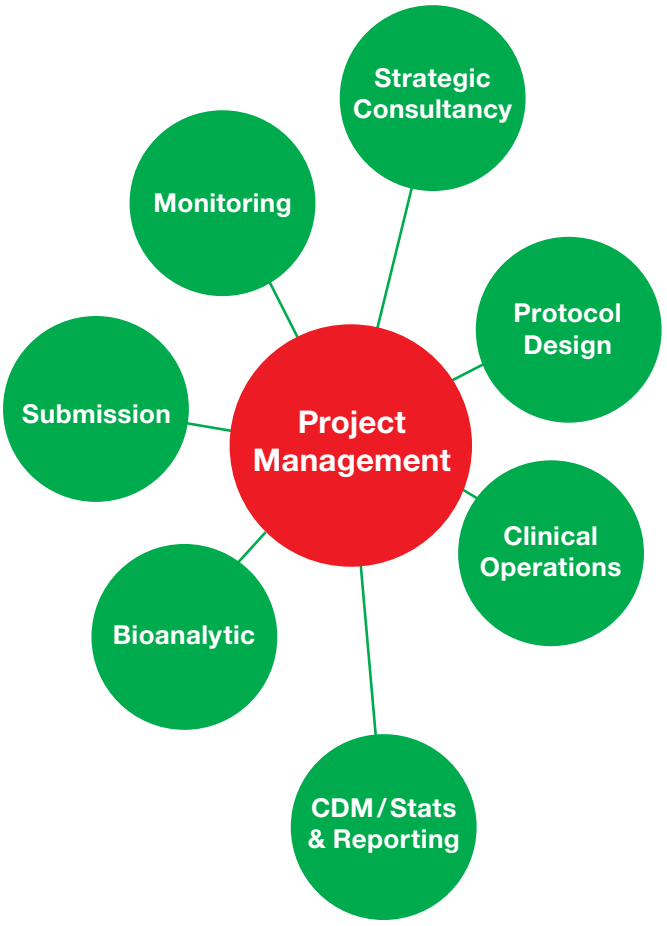

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the discovery that the physical and chemical properties of nanomaterials can also be altered, in an unpredictable manner, by changes in size or shape. This means a nanoparticle that is safe at 100nm could become highly toxic if it were to be broken down to 1nm pieces once *in vivo* (16) or, as previously mentioned, if it were to change shape.

Migrated nanoparticles can cause a number of other side-effects, such as blood clots, or become able to pass into the brain, which prompts questions about a relationship with neurological disorders (24).

Other Areas

Nanomedicine also presents many areas for concern outside of those seen in medicine, which are too complex to explore here. They include interactions with the environment and issues with the equality of distribution due to high manufacturing costs.

Possibly most disturbing of all are fears regarding the use of this technology to enhance cancers, rather than heal them, as well as the privacy of any information that may be gathered by such technology in the future (11).

Future Hope

While nanoparticle delivery of NSCLC treatment is, undoubtedly, a crucial step forward, there is a need for caution in all areas of its use. Until such a time when we are sure of the long-term effects on both humans and the environment, strict guidelines over experimentation should be devised, implemented and adhered to. Only by doing this can we hope to make nanomedicine part of the future of NSCLC treatment.

Part two of this article – to be featured in the next edition of *EPC* – will further discuss the controversy surrounding nanotechnology, including issues with data gathering, environmental impacts and manufacturing costs.

References

1. Visit: www.cancerresearchuk.org/cancer-info/cancerstats/types/lung/mortality/uk-lung-cancer-mortality-statistics#geog
2. Arany I and Safirstein RL, Cisplatin nephrotoxicity, *Seminars in Nephrology* 23(5): pp460-464, 2003
3. Non-small Cell Lung Cancer Collaborative Group, Chemotherapy in non-small cell lung cancer, a meta-analysis using updated data on individual patients from 52 randomised clinical trials, *British Medical Journal* 311(7,010): pp899-909, 1995
4. Devarajani P *et al*, Low renal toxicity of Lipoplatin compared to cisplatin in animals, nephrology and hypertension, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, US
5. Visit: www.uptodate.com/contents/cisplatin-nephrotoxicity
6. Boulikas T, Low toxicity and anticancer activity of a novel liposomal cisplatin (Lipoplatin) in mouse xenografts, *Oncol Rep* 12: pp3-12, 2004
7. Visit: www.hindawi.com/journals/jdd/2012/581363
8. Visit: http://regulon.com/lipoplatin.php
9. Boulikas T *et al*, Systemic lipoplatin infusion results in preferential tumor uptake in human studies, *Anticancer Research* 25(4): pp3,031-3,040, 2005
10. Visit: http://lipoplatin.com/encapsulation.html
11. The potential and pitfalls of nanomedicine. Visit: www.nanowerk.com/spotlight/spotid=1891.php
12. Maynard A, Nanoparticle safety – A perspective from the United States, in Hester RE and Harrison RM (eds), *Nanotechnology: Consequences for Human Health and the Environment*, The Royal Society of Chemistry, 2007
13. Stathopoulos GP *et al*, Comparison of liposomal cisplatin versus cisplatin in non-squamous cell non-small-cell lung cancer, *Cancer Chemotherapy and Pharmacology* 68(4): pp945-950, 2011
14. Visit: www.mhra.gov.uk/safetyinformation/generalsafetyinformationandadvice/adviceandinformationforconsumers/mymedicinefromlaboratorytopharmacyshelf/fromlaboratorytopharmacyshelf/index.htm
15. Visit: www.ganfyd.org/index.php?title=drug_withdrawals
16. Visit: www.ncbi.nlm.nih.gov/pmc/articles/pmc2695932
17. Visit: www.colorado.edu/honorsjournal/content/nanomedicine-small-particles-big-concerns
18. Cohen S, Human relevance of animal carcinogenicity studies, *Regul Toxicol Pharmacol* 21: pp75-80, 1995
19. Bhogal N and Combes R, TGN1412: Time to change the paradigm for the testing of new pharmaceuticals, *Altern Lab Anim* 34: pp225-239, 2006
20. O'Mathuna DP, Nanoethics: Big ethical issues with small technology, Continuum International Publishing Company, London, 2009
21. Pichot C, Reactive nanocolloids for nanotechnologies and microsystems, in Elaissari A and Hoboken NJ (eds), *Colloidal Nanoparticles in Biotechnology*, John Wiley & Sons, 2008
22. Tsuda A, What happens when you breathe in nanoparticles, in Chu J (ed), *Technology Review*, MIT Press, 7 December 2010
23. Oberdörster G, Oberdörster E and Oberdörster J, Nanotoxicity: An emerging discipline evolving from studies of ultrafine particles, *Environ Health Persp* 113: pp823-839, 2005
24. Hoet PHM, Inhalation of nanomaterials: Short overview of the local and systemic effects, in Simeonova PP (ed), *Nanotechnology – Toxicology Issues and Environmental Safety*, Springer, 2007

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