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Nanomedicine- is the wave cresting?

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Nanomedicine is playing an increasingly important role in pharmaceutical R&D, primarily in the form of nanoparticle-based delivery systems for drugs and imaging agents. By many quantitative measures the overall field of nanomedicine is flourishing. Over the last decade there has been an explosive growth of publications, patents, clinical trials activity and commercialization. Thus a search of the world patent literature using 'nanoparticle and drug' resulted in over thirty thousand hits, perusal of *ClinicalTrials.gov* using the term 'nanoparticle' found 122 current studies, while Nanowerk, a leading nanotechnology website, currently lists 356 companies with interests in nanobiotechnology or nanomedicine. Amidst this efflorescence of enthusiasm, however, a few notes of concern are beginning to be heard.

For example, an article provocatively entitled "Cancer nanomedicines: So many papers and so few drugs! " describes the difficult path for clinical development of nanoparticle-based drugs [1]. Similarly, a broad ranging overview of nanomedicine cautions against overpromising the benefits of this technology "Every month, articles claim novel/superior designer nanosized therapeutics, imaging agents, theranostics, and also nanomaterials to promote tissue repair. Most are, as yet, far from first in patient clinical trials, and many will never arrive there" [2].

All new biomedical technologies undergo a fairly predictable life cycle. As pioneering studies emerge there is a huge surge of enthusiasm in academia and in the commercial arena. After a time some of the problems and limitations inherent in the technology emerge, the initial enthusiasm is deflated, and many players leave the field. A few enthusiasts persist and eventually the technology finds its appropriate place in research and in clinical/commercial applications. It seems possible that nanomedicine is now verging on the inevitable phase of disillusionment.

Much of the academic research on nanomedicine in the USA has been funded by the National Institutes of Health; thus it is interesting to look at trends in NIH funding for this area. In the early 2000s NIH leadership recognized the growing importance of nanomedicine and initiated several major thrusts. In addition to traditional individual investigator (R01) type grants, various large-scale research programs were established. This includes the National Cancer Institute's Alliance for Nanotechnology in Cancer that has invested over $150 million, primarily in large centers of research excellence. Similarly, the National Heart Lung and Blood Institute's Program of Excellence in Nanotechnology (PEN) also supports several large research centers. Starting in 2005 the NIH Directors Office funded eight Nanomedicine Development Centers that addressed basic research issues in the field. All of these thrusts involved funding levels far in excess of traditional R01s and utilized monies that were sequestered for these specific projects. Currently, however, the NIH funding landscape for nanomedicine may be changing. The Director's office is no longer accepting applications in the nanomedicine area, while the future of the Alliance and PEN programs will be decided over the next year or so. Currently, all new submissions for nanomedicine grants must go through traditional NIH mechanisms where there is no sequestration of funds and nanomedicine proposals must therefore compete with proposals in other areas of

research. Thus, while overall NIH support for nanomedicine remains solid with over $300M in funding [3], other priorities such as the human microbiome, global health, and undiagnosed diseases are currently receiving targeted funding, while nanomedicine is not.

If there is a loss of enthusiasm for nanomedicine, especially as represented by nanoparticle-mediated drug delivery, this may be due to growing understanding of some of the constraints inherent in the technology.

Restricted biodistribution implies treatment limitations

Drug bearing nanoparticles are usually given by injection into the bloodstream and must cross the layer of endothelial cells that line blood vessels before encountering tissue cells. Typical 50–100 nanometer nanoparticles are far too large to cross the endothelial barrier in healthy tissues, excepting in the liver and spleen where there are gaps or fenestrations between the endothelial cells [4]. In some cancers the rapid growth of intratumoral blood vessels also results in endothelial gaps that allow nanoparticle delivery. However, it is clear that this effect does not occur in all cancers, and that there are many barriers to nanoparticle penetration into tumors [5]. Obviously it is important to be able to treat diseases based in a variety of tissues, and not just in the liver, spleen and a few select tumor types. At present this cannot reliably be accomplished with nanoparticles.

Efficacy vs Toxicity/Complexity vs Cost

Nanoparticle drugs present many challenges in terms of pharmaceutical development. The drug-nanoparticle moiety is far more complicated than the parent drug alone and thus formulation and scale up may be difficult and costly. Addressing these challenges would certainly be justified if major benefits were to accrue to patients. But is this happening? We cannot know the potential benefits of nanomedicines now under development. However, we can examine the early generation nanoparticle drugs that entered the clinic in the 1990s and 2000s such as the liposomal agents Doxil® and Ambisome® as well as the protein-drug nanocomplex Abraxane®. These agents are far more costly than their parent drugs (doxorubicin, amphotericin B, paclitaxel). Further, these nanodrugs made their mark in the clinic primarily by reducing toxicity rather than improving efficacy (see a discussion of Doxil® for example [6]). While reduced toxicity can certainly improve the quality of life for patients, relatively high cost coupled with minimal improvements in effectiveness may become an issue for nanomedicines.

The early nanodrugs distributed in the body passively, essentially in a manner that reflected their physical characteristics such as size and surface properties. Newer nanomedicines under development often include a ‘targeting’ moiety designed to promote association of the nanoparticle with a particular cell type or tissue. An excellent recent review discusses the advantages and problems associated with the development of targeted nanomedicines [7]. There are certainly technical challenges; for example, the addition of a targeting ligand may compromise the desirable ability of the nanoparticle to have a long lifetime in the circulation. Perhaps more importantly, targeted nanomedicines are likely to be extraordinarily costly. With national and private health care reimbursement entities increasingly using rigorous economic standards such as cost per quality-adjusted life year (QALY) [8], it will be important for the new generation of nanomedicines to provide improved therapeutic outcomes, such as extension of life in cancer patients, as well as reduced toxicity. As a reflection of this issue, a recent small scale clinical trial indicating that Abraxane® demonstrated no advantage over paclitaxel in breast cancer caused a considerable stir as some US payers reconsidered their reimbursement policies on Abraxane® [9].

Nanomedicine will continue to evolve and will no doubt eventually find an important place in health care. Nonetheless, it seems prudent to view the field with a critical eye, to be aware of its limitations as well as its capabilities, and not to oversell its promise.

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