

# The impact of future trends in new sciences on the practising pharmacist

In this sixth article leading to a consultation among members about the Royal Pharmaceutical Society's Pharmacy 2020 project, Molly Stevens, of Imperial College London, and Clive Roberts, of Nottingham school of pharmacy, look at how new sciences will affect the future for pharmacy

The pace of new discoveries in biotechnology and health care and even the appearance of whole new fields of endeavour in recent years have made for an exciting and challenging time for pharmacists. The increasing demands of understanding how modern medicines work at the molecular level, the shift towards predictive, preventive and personalised health care and challenges from nanotechnology and stem cell technology have added to the need for pharmacists to remain the experts in medicines.

## Introduction to nanotechnology

Nanotechnology is the ability to understand and control matter at the smallest scales, from around 100nm down to the dimensions of atoms. The concept for technologies at this scale came in the late 1950s with Richard Feynman's lecture "There's plenty of room at the bottom". Feynman noted: "The principles of physics, as far as I can see, do not speak against the possibility of manoeuvring things atom by atom, . . . it would be, in principle, possible . . . for a physicist to synthesise any chemical substance that the chemist writes down." Almost 50 years later nanotechnology has proven this possible, whether this is by traditional "top-down" approaches which involve standard lithographic procedures pushed towards their physical limits or "bottom-up" methods which use systems capable of self-assembly into functional supramolecular structures. Inspiration for this latter approach can be drawn from biology, where for instance our own skeletons are an example of a self-assembling nanocomposite material.

Huge sums are being invested in nanotechnology research and development, £0.5bn in 2000, £4.7bn in 2004 and a predicted £15bn in 2008. What makes nanotechnology so attractive? It is not simply a matter of scale, but that the properties of matter can be different when compared with those with which we are familiar. Materials can be stronger, lighter, more soluble, less hygroscopic, or become unusually optically or electrically active. A commonly quoted example compares the time for a grain of sand to dissolve in water (34,000,000,000 years) to that of a nanometre sized grain (one second). Such radical properties, here based upon the massively increased surface-to-volume ratio of a nanoparticle, are the basis on which many believe nanotechnology will revolutionise a wide range of markets, especially materials (where a major impact has already occurred), electronics and health care.



## Nanotechnology in health care

Traditionally nanotechnology in pharmacy has been associated with drug delivery, where the size of the delivery vehicle, whether it be a liposome, a polymer or even a metallic nanoparticle and its consequent ability to evade many of our bodies' natural defences has been the main attraction. We have recently seen the launch of the first nano-delivery system (DOXIL; Ortho-Biotec), a reformulated version of the anticancer agent doxorubicin. Here the drug is encased within polyethylene glycol (PEG)-coated liposomes less than 200nm in diameter. Because of the sustained release of the drug from the liposome and its long circulation time from the "stealth" ability conferred by the PEG, intravenous treatment is only required every four weeks. The use of PEG to mask a drug from our natural defences has also been used for antibody based therapeutics. Other delivery routes have also benefited. For example, VivaGel — a topical anti-HIV formulation — is one of the first drug products based upon nanoscale molecules called dendrimers (hyperbranched polymeric macromolecules, 2–10nm in size). Looking ahead, a recent report suggests that the efficiency of inhaled drug delivery could be improved eight-fold using magnetic fields to guide drugs mixed with magnetic nanoparticles.

Although the lead time required to bring products to the market in the health care sector is longer than in other areas, it is clear that the steady stream of launches which led to 38 products on the market in 2004 is shortly to increase dramatically, and not only in drug delivery. The implications of nanotechnology go much further, including for example: superparamagnetic iron oxide nanoparticles for magnetic resonance imaging; nanopowders to increase bioavailability of poorly soluble drugs; wound dressings and medical devices using antimicrobial nanosilver; magnetic and optically active materials for cancer treatment; nanohydroxyapatite for implant coatings and bone substitution; and nanosensors for point-of-care diagnostics.

Some of the most far-reaching consequences of nanotechnology we can foresee

are still in the research laboratory. Although the idea of nano-engineered robots circulating our systems like mini-submarines killing diseased cells are fantasy, the ability to make use of and modify biomolecular machines and motors — the proteins and nucleic acids that make life possible — is real. For example, recently, a synthetic molecular motor capable of autonomous nanoscale transport inspired by bacterial pathogens was demonstrated. This new biomolecular motor operates by polymerising a double-helical DNA tail and is hence powered by the free energy of DNA hybridisation. Other researchers are using the coded nature of DNA binding to assemble large complex structures, even being able to produce letter shapes which form spontaneously. The exact applications of such work may not be obvious but these are clearly important steps on the path to radical new applications in health care.

## Stem cells

Stem cell research has already provided some outstanding contributions to our understanding of developmental biology and has offered much hope for the regeneration of diseased or injured tissues. Stem cells, whether embryonic stem cells or tissue-derived stem cells (also known as adult or somatic stem cells), can undergo self-renewal as they have a higher capacity to proliferate than specialised tissue cells. They can also differentiate into other cell types such as more functionally specialised mature cells. Stem cells have the potential to revolutionise current medical practice by a variety of methods including cell replacement therapies, tissue engineering and the activation of resident *in vivo* stem cells. Application of stem cells in the area of regenerative medicine was covered previously (*PJ*, 3 December 2005, p695).

Another application where pharmacists may see developments with stem cells in the near future is within the pharmaceutical industry where stem cells can enable the development of models of a number of diseases and thereby assist in more effective screening of potential new chemical entities. Two of the leading causes of failures in preclinical development of new therapeutic drugs are critical safety issues such as hepatotoxicity and cardiotoxicity. Animal models of cardiotoxicity, for example, cannot always accurately predict clinical outcomes and have some limitations. In instances where the drug's effect on the QT interval is not well established then a detrimental prolongation of the QT interval

could lead to torsade de pointes, a rare but dangerous ventricular arrhythmia. Using human cardiomyocytes (heart cells) can provide a useful *in vitro* model system but their use in high throughput safety evaluation is hindered by a lack of healthy donors. In contrast, human stem cells with their ability to self-renew and differentiate into cardiomyocytes may provide a larger number of cells with which to conduct these important *in vitro* safety tests. This use of stem cells is not limited to cardiotoxicity and the human cells may also generate suitable models for hepatotoxicity, genotoxicity and reproductive toxicology screens among others, and help improve the selection of lead candidates and reduce drug failures in later stages of development.

A hot topic in the stem cell field is the creation of human-animal hybrid embryos and their recent approval for use in research in the UK. Researchers will be able to generate any type of interspecies hybrid embryo for research if they acquire a licence, provided the embryos are not allowed to develop beyond two weeks and are not implanted into a womb. This latest development means that it will be possible to make stem cells from people with a specific disease, by transferring, for instance DNA from the skin of a patient to an animal egg (eg, a cow or other species). Importantly this will allow the study of the effect of drugs on the diseased biochemistry of the human cell. There is currently a lack of human egg donors for this purpose and this new approach will help in the study of new treatments for many diseases.

### Personalised medicine

Another emerging field which will impact on pharmacists is the advent of "personalised medicine", enabled by the genomic revolution. Indeed, the human genome project has led to the identification of over 32,000 genes in human cells and, through the burgeoning field of pharmacogenetics, it is increasingly apparent that the effectiveness and toxicity of drug regimens vary from patient to patient as they are influenced by the genetic make-up of the individual. For example, using genomics or transcriptomic analysis to identify changes at the mRNA level in patients with systemic lupus erythematosus has led to the identification of a subgroup that may benefit from new therapeutic options.

It is likely that in the future pharmacists will see more drug treatments tailored to the patient following screening for biomarkers which may help guide targeted therapy and predict or assess therapeutic response. Biomarkers can be defined as molecules that are measurable indicators of a specific biological state (for example that may affect drug therapy or be of use for therapeutic monitoring), and that are also relevant to the risk of contraction, the presence or the stage of disease. Biomarkers can take many forms and may be detected through genomics or proteomics approaches (the latter measuring the collection of proteins expressed in a given cell

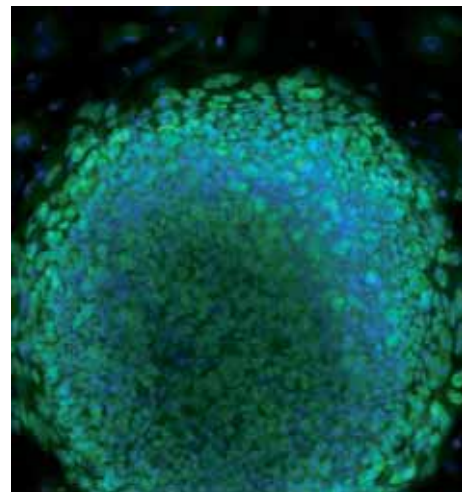
type, tissue or body fluid). However it is now well-established that changes at the mRNA level do not capture most of the variations at the protein level. Screening using proteomics may yield better clinical predictors as the protein domain is likely to be the most ubiquitously affected in disease, response and recovery. Currently, however, screening using proteomics suffers from a relative lack of sensitivity compared to detection of mRNA.

Biomarkers have been identified for several different forms of cancer, Alzheimer's disease, diabetes, neurodegeneration, metabolic diseases, tissue damage and many other conditions. However inherent problems in the lack of specificity of individual biomarkers is favouring the use of multiple biomarkers in combination, and for this there is a pressing need for the elucidation of better biomarkers and technological developments in analytical capability. Furthermore there is as yet no coherent pipeline from biomarker discovery to validation and incorporation into point of care testing kits, although this is likely to change in the future. As an example of the slow route to market, one can point to the fact that the use of DNA microarrays for cancer diagnosis and prognosis was proposed over 10 years ago but appropriate microarray diagnostic kits are yet to be approved by the US Food and Drug Administration. Although many genomic and proteomic approaches will be most suitable for blood tests, others will sample other body fluids such as saliva and urine and the pharmacist may thus well be involved in the administration of these.

Chronic diseases like cancer, diabetes, hypertension and heart disease remain major issues in public health and are likely to do so over the coming years. Even for these chronic diseases, all of which have a genetic basis and identified biomarkers, the important role that environmental influences play mean that the pharmacist's role in counselling and promotion of "healthy living" will remain important.

### Public perception and concern

The "nano" word is firmly embedded in the national consciousness and has become an area of public debate and often concern. From fanciful tales of self-replicating "nanobots" engulfing the world to legitimate concerns as to the effect of nanoparticles used in such everyday products as suncreams, nanotechnology is rarely out of public view. Yet clearly nanotechnology brings substantial benefits and it is important that these benefits are balanced against perceived and real risks of nanotechnology. Similarly, stem cell research has in the past decade justifiably gained one of the highest scientific profiles both in the medical community and the general public. This profile is undoubtedly fuelled not only by the therapeutic (and therefore financial) potential but also by the emotive ethical and political implications. In the application of genomics and proteomics for disease screening there will certainly be a group who would rather not be informed that they have a life-threatening or incurable disease and the



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A colony of stem cells

question over who would own an individual's proteomic or genomic profile and issues over confidentiality are still unresolved.

As part of this picture it will become increasingly important that pharmacists in all sectors of practice appreciate the radical potential of nanomedicines, stem cells, genomics and proteomics, and can communicate in a balanced and informed manner the positive benefits and potential risks they bring. To aid this, it is critical that advances in these fields move forward within a framework of suitable regulation and open public debate. The strong regulatory environment in the pharmaceutical profession has meant that it is at the forefront of this process. A number of influential reports have led to this position, including the FDA's Nanotechnology Task Force 2007 report which notes that "the emerging and uncertain nature of nanotechnology and the potentially rapid development of applications for FDA-regulated products highlight the need for ensuring transparent, consistent, and predictable regulatory pathways". The need for ongoing debate and discussion between scientific professionals and the Government was no more apparent than just a few weeks ago in the Parliamentary Committee's backing of the human-animal hybrid embryos following strong support of the research from the professional scientific community.

### Conclusions

The future of health care is closely intertwined with developments in nanotechnology, stem cells, genomics and proteomics. Nanotechnology is here with us today and is being used in an evolutionary manner to improve the properties of many therapeutics and healthcare products. The application of stem cells in regenerative medicine and in drug screening is set to grow. Advances in genomics and proteomics are fuelling the shift towards predictive, preventive and personalised medicine. How these technologies will evolve and be used safely for all our benefit will be one of the great scientific adventures of the first half of the 21st century and one in which pharmacists will play an important role.