The drug discovery industry has become such a competitive market that it continually faces a challenge to find better drug discovery technologies. This industry has to discover and develop innovative medicines for a wide range of diseases in a marketplace that is likely to experience growing regulatory challenges, pricing pressures and various other bottlenecks. Currently, nearly all pharmaceutical companies follow common technology processes for discovering drugs. These include, cloning and expressing human receptors and enzymes in formats that allow high throughput, automated screening and the application of combinatorial chemistries. The genomics and proteomics revolution has delivered massive amounts of data about life's molecular components, giving the drug discovery industry more qualified targets and leads than ever before. In a drive to improve productivity and to sustain market share, pharmaceutical and biotechnology firms have over the years invested billions of dollars in innovative technologies that are able to accelerate the drug discovery and development processes. Applications range from target identification and validation to clinical trials, administration, marketing and sale-up.

In the last decade, technology changes have enabled the process of drug discovery to evolve into a system where new lead molecules can be rapidly found against novel, and sometimes, difficult targets. While automation steps toward miniaturisation and robotics-based strategies have greatly increased throughputs in compound synthesis and screening, they have merely begun to scratch the surface. The introduction of microarrays and lab-on-a-chip (LOC) technologies have already revolutionised the drug discovery process. These innovative technologies generate high-value data at a lower cost and enable researchers to conduct experiments more efficiently.

In terms of drug discovery and development, the role of nanotechnology currently lies in improving diagnostic methods, developing improved drug formulations and drug delivery systems for disease therapy. The breakthrough format of nanotechnology offers innovative solutions, giving researchers greater analytical capacity, improved data quality and at the same time consuming less sample volume in the storage and screening of molecular, cell and tissue libraries. The advances in the technology are now beginning to overcome the initial challenges of insufficient throughput, unreliable data and various other issues. This article will focus on the principal trends and the implications on drug discovery.

The role of nanotechnology in drug discovery

By Dr Amarpreet S Dhiman

In terms of drug discovery and development, the role of nanotechnology currently lies in improving diagnostic methods, developing improved drug formulations and drug delivery systems for disease therapy. The breakthrough format of nanotechnology offers innovative solutions, giving researchers greater analytical capacity, improved data quality and at the same time consuming less sample volume in the storage and screening of molecular, cell and tissue libraries. The advances in the technology are now beginning to overcome the initial challenges of insufficient throughput, unreliable data and various other issues. This article will focus on the principal trends and the implications on drug discovery.
information in a condensed timeframe, which
minimise the guesswork involved in target, lead
and drug candidate selection. And now, even more
pioneering technologies, such as nanotechnology,
are set to streamline the drug discovery process
further, through miniaturisation, automation,
speed and reliability of assays by working at levels
far smaller than conventional micro-arrays.

The foundations of nanotechnology emerged
over many decades of research in many different
fields. In 1959, the great physicist Richard
Feynman suggested that it should be possible to
build machines small enough to manufacture
objects with atomic precision. His talk, 'There's
Plenty of Room at the Bottom', is widely consid-
ered to be the foreshadowing of nanotechnology.
Among other things, he predicted that information
could be stored with amazing density. From the
1970s onwards, Eric Drexler published many sci-
entific papers introducing the term 'nanotechnolo-
gy', and highlighting ways to manufacture
extremely high-performance miniaturised
machines. Drexler realised that the chemical man-
ufacture of complex products, including additional
manufacturing systems would become a very pow-
erful technology.

Nanotechnology, as its name applies, refers to
research and technology development at the atom-
ic, molecular and macromolecular scale, leading
to the controlled manipulation, and the study of
structures and devices with length scales in the 1
to 100 nanometers range. Objects at this scale,
such as ‘nano-particles’, take on novel properties
and functions that differ markedly from those seen
in the bulk scale. The small size, surface tai-
lorability, improved solubility, and multifunction-
ality of nano-particles open many new avenues of
research for biologists. The novel properties of
nano-materials offer the ability to interact with
complex biological functions in new ways that
operate at the very scale of biomolecules. This rap-

Table 1: Segmentation of the nanotechnology market

| NANO-ENABLED TOOLS | NANO-PARTICLES/ MATERIALS | NANO-ENABLED DRUGS |
|-------------------|--------------------------|-------------------|
| Atomic force microscopy | Quantum dots | Examples include: |
| Nano-mass spectroscopy | Shells | Abraxane |
| Dip-pen nanolithography | Bars | RenaZorb |
| Nano-arrays | Dendrimers | Antimicrobial emulsions |
| | | Antioxidants and fullerenes |

Nanotechnology can be broadly classified into
to three groups, namely, ‘Nano-enabled tools’,
‘Nano-particles’ and ‘Nano-enabled drugs’. These
groups can then be further segmented into various
technologies that contribute to the nanotechnology
market, as shown in Table 1.

The central paradigm in proteomics studies has
been to identify differential protein levels in
healthy and diseased cells, characterise these

The earliest commercial nanotechnology used
for pharmaceutical applications has been the
Atomic Force Microscope (AFM). Using a silicon-
based needle of atomic sharpness, this approach
was first used to image the topography of surfaces
with atomic-scale precision. The ultra-fine tip
scans the sample and creates a three-dimensional
image of the surface. The AFM is fast becoming
the principal technology that scientists and
researchers use, allowing researchers to directly
view single atoms or molecules and manipulate
samples at the nanometer scale. While AFM is
invaluable for imaging objects at the nanoscale in
such areas as life science, materials science, elec-
trochemistry, polymer science and biophysics, until
recently they have been used in techniques to
greater understand the chemical dynamics of how
cells react to stimuli, which may prove particularly
significant for drug discovery.

The central paradigm in proteomics studies has
been to identify differential protein levels in
healthy and diseased cells, characterise these
proteins and determine the protein’s role in biochemical pathways. These proteins can then serve as diagnostic markers and potential drug targets. At the forefront of these emerging and growing technologies are protein and DNA micro-arrays that allow the highly specific capture and analysis of a large number of proteins expressed in various cell types exposed to given perturbations in a high throughput manner. However, currently available micro-array technologies suffer from certain limitations that prohibit the exploitation of the full range of drug discovery applications. The next step of evolution is the creation of nano-arrays, an ultra-miniaturised version of the traditional micro-array that can actually measure interactions between individual molecules down to nanometer resolutions. Using nano-array technology, very small quantities of individual proteins can be effectively screened against a large set of drug targets. In addition, nano-arrays can be incorporated as sensors in ways that are impossible with larger micro-arrays.

Nano-materials are developed to address the need for greater sensitivity in high throughput screening. Nano-particles (dots, bars, dendrimers or colloids) provide molecular labels that are highly stable, readily multiplexed and comparable in size to the molecular components of interest. Nano-particles exist in the same size domain as proteins making nano-materials suitable for bio-tagging or labelling. However, in order to interact with a target, a biological or molecular coating or a layer acting as a bioinorganic interface is required to be attached to the nano-particle. The majority of commercial nano-particle applications in medicine are geared towards drug discovery and delivery. Nano-particles are slowly replacing organic dyes in applications that require high photo-stability as well as multiplexing capabilities. Used as another form of molecular tagging, nano-bars are constructed from alternating layers of reflective metals which can be optically scanned as literal bar codes to differentiate molecular species. Such systems offer advantages over conventional labelling in that there are a large number of different labels that can be constructed, multiplexing is possible, and the signal is long-lived.

Still at an embryonic stage of development, nanotechnology has already enabled new formulations for drugs that are bringing clinical benefits to patients. For instance, RenaZorb, developed from a lanthanum-based inorganic active pharmaceutical ingredient (API) based on patented ‘growth-in-film’ nanotechnology, is shown to provide phosphate control in kidney dialysis patients. Similarly, the FDA-approved Abraxane has indications for the treatment of metastatic breast cancers. Abraxane combines the active drug Paclitaxel with a natural protein called albumin into a nano-particle 1/100th of the size of a red blood cell, avoiding the need for any solvent. Other drugs that are in R&D pipeline or in the regulatory approval stage are those for the treatment of skin disorders and infections.

**Benefits versus impact**

The anticipation that treatments for diseases such as cancer will be revolutionised with the advent of nanotechnology-based products such as nano-arrays and dendrimers is stimulating research in nano-medicine. The realisation is that the nanoscale has certain properties to solve important medical challenges and to cater to unmet medical needs is a factor driving research in nano-medicine (Figure 1). Nanotechnology has the potential to prolong a disease-free lifespan. In addition, for many chronic diseases and disorders, nano-medicine offers the potential and hope for a cure. Some of the major factors driving the expansion of nanotechnology-based solutions in drug discovery include: identification of novel chemical structures, ability to manipulate and track cells on the nanoscale due to advances in microscopy, increased government funds earmarked for nanotechnology, significant and growing interest from the venture capital community, and the rapid proliferation of nanotechnology start-up companies.

However, nanotechnology still has a long way to go. With a global investment estimated to be just over $8.5 billion in 2005, revenues generated for the total world market for nanotechnology-based solutions in drug discovery was estimated to be less than $700 million in the same year. The market is expected to grow in double figures and reach an astonishing $2.5 billion by 2012. Nano-enabled tools, such as nano-arrays and nano-mass spectrometry, among others, will offer the largest opportunities along with nanoparticle solutions (Qdots, Dendrimers, etc) and nano-enabled drugs also showing significant growth. Traditionally, funding for emerging technologies has been difficult to secure. However, a significant amount of funding has been allocated to nanotechnology, in particular nano-medicine. As nanotechnology has a broad interdisciplinary nature and has demonstrated its ability to advance various areas of healthcare including diagnostics, therapeutics and drug discovery, the attention has shifted to attract funding.
Governments are making funding available for nanotechnology research, while the interest from the venture capital community continues to grow. A key driver in the creation of start-up companies in this field would be investment from both public and private sources that will determine the success of this industry.

The demand for rapid drug discovery and for improved drug therapeutics has witnessed the formation of a number of companies working in the field of nanotechnology-based solutions. Although the industry comprises many start-ups since the integration of nano-medicine, companies that are in the best position to benefit from the move towards nanotechnology-based solutions in drug discovery are major microfluidics and LOC companies. Such companies include Aclara Biosciences, Agilent Technologies, Caliper Life Sciences, Cepheid, CombMatrix Corporation, Eksigent Technologies, Gyros, Nanogen and Nanostream. Leading corporations such as AstraZeneca, BD Biosciences, Genentech, GlaxoSmithKline, Invitrogen Corporation, Johnson & Johnson, Merck and Pfizer are also expected to fare well since they have collaborative relationships with the likes of 3DM, Alnis Biosciences, C Sixty and Quantum Dot Corporation. The latter is a global leader holding several key international patents on semiconducting nano-crystal technology with its principal technology Qdots® being used for high-throughput screening.

Companies such as 3DM, American Pharmaceuticals, BioCrystal, CrystalPlex Corporation, C Sixty, Evident Technologies, NanBio Corporation and Nanosphere are also expected to experience further opportunities in the next decade because they offer new solutions for drug delivery and diseases prevention, as well as drug discovery.

**Overcoming the obstacles**

It is worthwhile to note that nanotechnology is by no means a ‘sure thing’ as there is still a tall ladder to climb to reach the Holy Grail. Numerous challenges associated with nanotechnology relate to the market-driven needs within the industry. The majority of nanotechnology-based solutions in drug discovery are still in the early phases of research and development (R&D). In order to move to practical applications in the commercial sector, nanotechnology will have to perform at high accuracy levels, achieving higher levels of throughput compared to current standard micro or macroscale, automated instruments. It is true to say that any new innovative technology brings expectations and high hopes. Although, this could benefit companies in the deployment of additional funds and financial resources, a lack of significant progress, commercial bottlenecks or any other regulatory barriers could dash hopes, as well as credibility. Like a decade ago, when high throughput screening (HTS) was being touted as the answer to improving productivity in drug discovery, leading
to the boom in Ultra HTS (UHTS) and high-speed automation, which has now begun to decline, having not lived up to its hype. Some would argue that one is not likely to see nanotechnology-based products for years, and it is likely to take even longer for any ‘nano’ company to be in line with current ‘micro’ companies such as IBM, Intel or Microsoft. Furthermore, the majority of target customers (which are predominantly expected to be pharmaceutical and biotechnology companies) may be reluctant to spend any more on new systems, unless the advantages are significant and apparent.

One of the more major aspects is the long-term stability of nanotechnology products. In particular, nano-particles and nano-materials used for drug discovery applications can become a cause for concern if they degrade too rapidly or they remain in the body for long periods of time, and thus, need to meet optimum levels of stability. The ability of nano-materials to interact with biological organisms leads to the possibility that they may be harmful to humans and the environment. Current understanding of the potential toxicity of nano-particles is limited, but research indicates that some of these products may enter the human body and become toxic at the cellular level, in various body fluids, tissues, and/or organs. For instance, nano-particles composed of metals such as selenium, lead and cadmium can be toxic to organisms if these metals manage to leech from the particles. Moreover, it has been reported that water-soluble fullerene molecules...
Nanotechnology can cause brain damage in a species of freshwater fish called ‘largemouth bass’. Similarly, dendrimers have been shown to cause osmotic damage, activate the clotting and complement systems and even result in the removal of cell membranes. The impact of nano-particle interactions with the body are dependent on their size, chemical composition, surface structure, solubility, shape, and how the individual nano-particles amass together. Nano-particles may modify the way cells behave and potential routes of exposure include the gastrointestinal tract, skin and lungs. To ensure optimum safety and limit exposure, a strategy of key elements for toxicity screening should include the physical and chemical characterisation of nano-materials, tissue cellular assays and animal studies.

Among other barriers, such as technical issues, lack of standardisation, uncertainty, public awareness, resources, there are also communication and cultural barriers between nanotechnology research communities and the pharmaceutical industry that have hindered collaborations and delayed the progression of nanotechnology-based solutions in drug discovery. Nanotechnology has an extremely interdisciplinary character having a broad range of disciplines. It is this wide range of disciplines which can even make discussions complicated and result in a definite lack of a common language. In order to overcome these barriers, the industry must increase its awareness and its potential to encourage dialogue between nanotechnology and other communities. The interests of nanotechnology merge from biologists, chemists, genome engineers, biotechnologists, and so on. By collaborating together extensively, the complexity of combining disciplines in nanotechnology would generate new businesses.

What does the future hold for nanotechnology?

Although the benefits of nanotechnology are huge, there are certainly many hurdles ahead. Nanotechnology-based solutions in drug discovery are beginning to generate substantial new insights into how biological systems function, and likewise will lead to the design of entirely new classes of micro- and nano-fabricated devices and systems. The use of micro-fabrication as a method of miniaturising multidisciplinary devices is just beginning to reach the life science industrial community. Even though many of the ideas developed in nano-medicine might seem to be in the realm of science fiction, nanotechnology presents some unique opportunities. Nanotechnology will soon allow many diseases to be monitored, diagnosed and treated in a minimally invasive way and thus it holds great promise for improving health and prolonging life. Whereas personalised medicine brings together better diagnosis and prevention of disease, nanomedicine might very well be the next breakthrough in the treatment of diseases.

Dr Amarpreet Dhiman joined Frost & Sullivan in 2004, focusing in the area of Drug Discovery and Clinical Diagnostics for the European Healthcare Practice. His role involves analysing European and Asia Pacific driven markets in terms of market development and emerging technology analysis, consulting with key opinion leaders, and project and article writing. Prior to joining Frost & Sullivan, Amarpreet worked as a Consultant Product Manager and Project Coordinator for a growing Dental Company and Orthopaedic Company.