NANOMEDICINE

September 2005

Nanomedicine – Summary (1)

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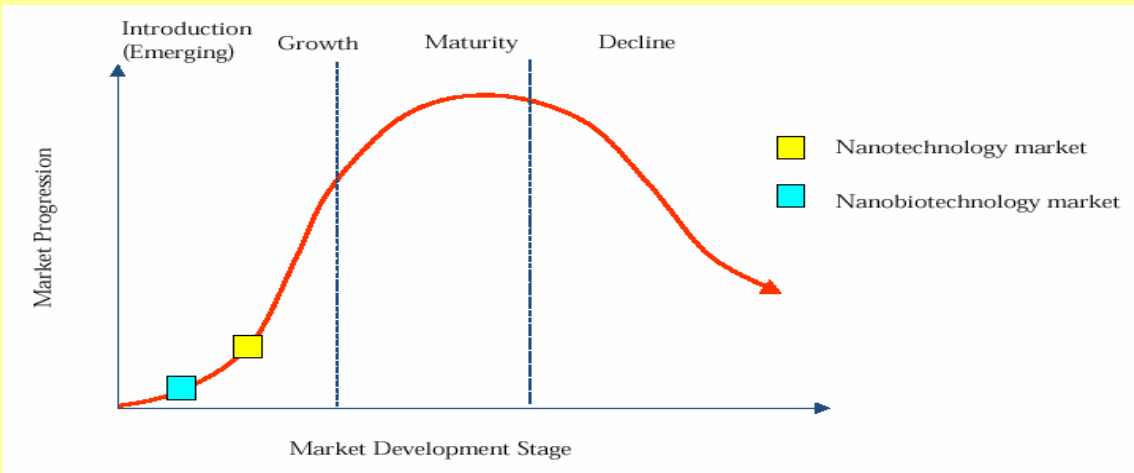
Definition

- The term nanomedicine encompasses the application of nanotechnology, defined as research and development within the length scale of 1-100 nanometres (10^{-9} metres, or 1/80,000 the diameter of a human hair), to the prevention and treatment of disease in the human body.

Market Dynamics

- Segmented market
  - Short or near term goals, occurring within the next five years, which will bring performance gains for existing diagnostics, therapeutics and pharmaceuticals
  - Long term goals, occurring in the timeframe five to ten years, which will bring novel and innovative solutions to current unmet clinical requirements
- Short term market (primarily sales of nanomaterials) generated revenues of $750 million in 2004
- CAGR of 15.5% over the next 6 years
- The longer term market is currently a virtual one as no products have been approved



- Nanomedicine can be described as an emerging market, which is less developed than the larger and more mature nanotechnology market.

Nanomedicine – Summary (2)

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Key Nanomaterials

- Nanoparticles
- Fullerenes (Buckyballs)
- Carbon Nanotubes (CNTs)
- Dendrimers

Key Applications and Intellectual Property

- Drug Delivery and Therapeutics
- Diagnostic Genetic Testing
- Imaging and Sensors
- Implants, Scaffolds and Tissue Repair
- Sensory Aids
- Surgical Aids

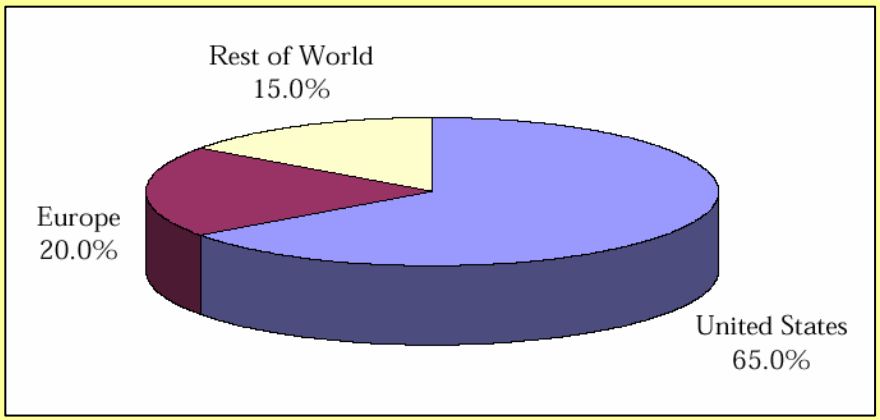
Challenges

- Hype
- Materials and manufacturing costs
- Safety concerns
- Lack of Global Standards and Regulations
- Lack of Pharma investment

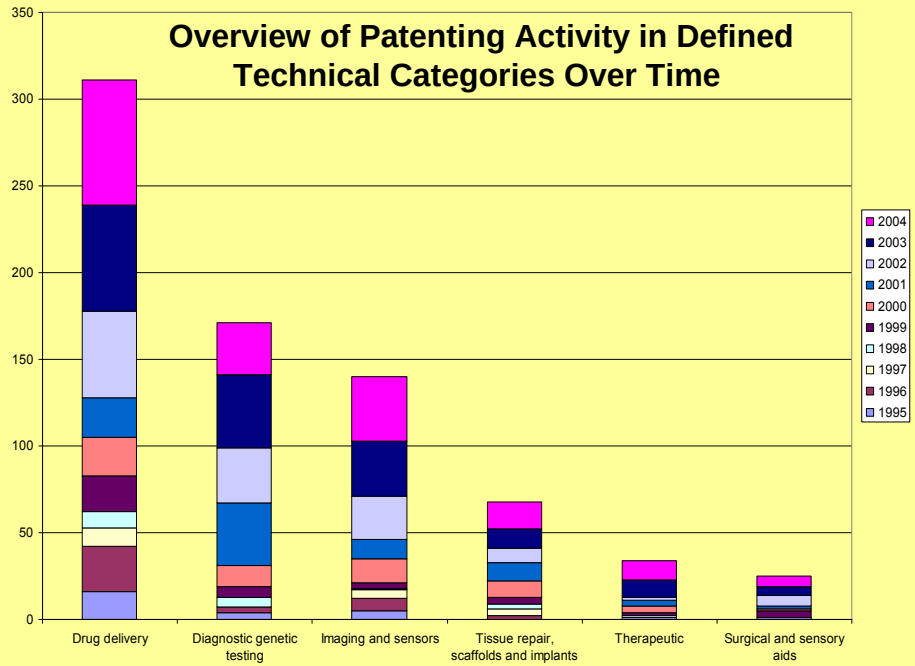
Drivers

- Miniaturisation
- Strong Government investment
- Innovative solutions to unmet clinical needs
- First products on the market
- Extended drug lifetimes

- The US has a leading position with regards to both funding and patenting activity in nanomedicine



Geographical distribution of nanomedicine funding



Nanomedicine – Summary (3)

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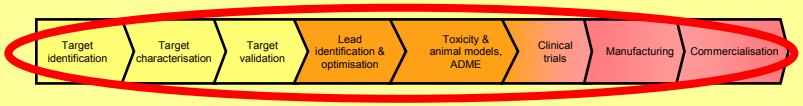
Value chain and Business models



- Nanomedicine has the capacity to impact at all levels of the value chain
- Whilst most of the long term opportunities are still at the validation and proof of concept stage, there have been some nanomedicine-related reformulation of existing drugs strategies that have been approved and are already on the market

Business models

- Long term opportunites primarily driven by academic or SMEs.
- Marketed products via collaborations with large Pharmas and Biotechs.

Scottish Context

- Good academic research base in the area of nanotechnology. Some initial forays into nanomedicine
- Strong skills base in many of the scientific disciplines required to optimally impact upon nanomedicine
- Two nanomedicine-related companies
- Institute of Nanotechnology
- Institute of Occupational Medicine

Current and expected players & stakeholders

- Elan, Abraxis, Novavax, Nucryst, NanoBio Corp, Flamel, Starpharma, Quantum Dot Corporation, Nanosphere, Luna Innovations, MediRad, Liquidia Technologies, CSixty Inc, Dendritic Nanotechnologies, Nanospectra, Orthovitra, Angstrom Medica, pSivida
- Stakeholders include pharmaceutical companies, biotech companies and academic research groups

Market Demand

- Near term goals will be to offer lifecycle improvements to existing diagnostics, therapeutics and pharmaceuticals.
- Long term goals will be driven by requirements for ever-improving functionality, treatments and therapeutic regimens, as well as truly novel products to treat and diagnose currently unmet clinical requirements.

Foresighting

Opportunities

- Short term.
  - Reformulations of existing drugs, allowing improved dosing regimes, increased efficacy and reduced toxicity side effect profiles.
- Long term.
  - Convergent site-specific targeted drug and/or gene delivery with additional imaging / contrast agents.
  - Real time *in vivo* monitoring of the internal chemistry of the body, enabling early detection and diagnosis of undesirable conditions, potentially coupled to a method of administering the relevant therapeutic, using a convergent theranostic (therapeutic/diagnostic) approach.
  - Improvements in safety, strength and viability of implants combined with reduced immunorejection, or nanomedicine-related benefits to regenerative medicine.

Barriers

- Identification of correct niche areas will be critical in this competitive area
- Best proposals will utilise partnerships and the formation of cross functional scientific teams capable of communicating a convergent vision.

Contents

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- **Nanomedicine:**

  *"The application of **nanotechnology** to the **prevention and treatment of disease in the human body**".*

  US Government's National Nanotechnology Initiative (NNI)

- **Nanotechnology:**

  *"Research and technology development at the atomic, molecular and macromolecular levels in the length scale of approximately **1–100nm** range, to provide a fundamental understanding of phenomena and materials at the nanoscale and to create and use structures, devices and systems that have novel properties and functions because of their small and/or intermediate size".*

  US Government's National Nanotechnology Initiative (NNI)

- These definitions are very broad and can lead to manipulation of what we believe is the true advantage of nanomedicine – a technology that can provide ***new*** products rather than the manipulation of existing products.
- An alternative outlook is “to consider not only a product’s size, but also the contribution of size to how the product works”, Ajaz Hussain, Deputy Director of the Office of Pharmaceutical Science at the FDA.
- These contrasting definitions lead to differing viewpoints on what constitutes a “true” nanomedicine product and hence the difficulty in analysing the current market status and forecasting the future nanomedicine opportunities and timeframes.
- For this reason, for the remainder of this report we will define two distinct potential markets:
  - ***Short or near term goals*** which will bring **performance gains** for existing therapeutics / pharmaceuticals.
  - ***Long term goals*** which will bring **novel and innovative solutions** to current unmet clinical requirements.

Nanotechnology

- Was first described in 1959 by Dr Richard Feynman (Nobel Laureate in Physics, 1965) in his famous lecture to the American Physical Society entitled “There’s plenty of room at the bottom”.
- Produces nanostructures that are similar in size to biological molecules (see following pages).
- Derived nanostructures are synthesised from both inorganic heavy metals and/or organic polymers, carbohydrates, lipids, or DNA.
- Enables the miniaturisation of industrial applications/artificial assemblies to a previously inaccessible size.
- Allows the analysis of the physical, chemical & biological properties of molecules and structures inside living cells with similar quantum mechanical properties of atomic interactions.

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Comparative Sizes of Nanomaterials and Biological Structures

- Nanoparticle 1–100nm
- Fullerene 1nm
- Quantum Dot 8nm
- Dendrimer 10nm

- Atom 0.1nm
- DNA (width) 2nm
- Protein 5 – 50nm
- Virus 75 – 100nm
- Materials internalized by cells < 100nm
- Bacteria 1,000 – 10,000nm
- White Blood Cell 10,000nm

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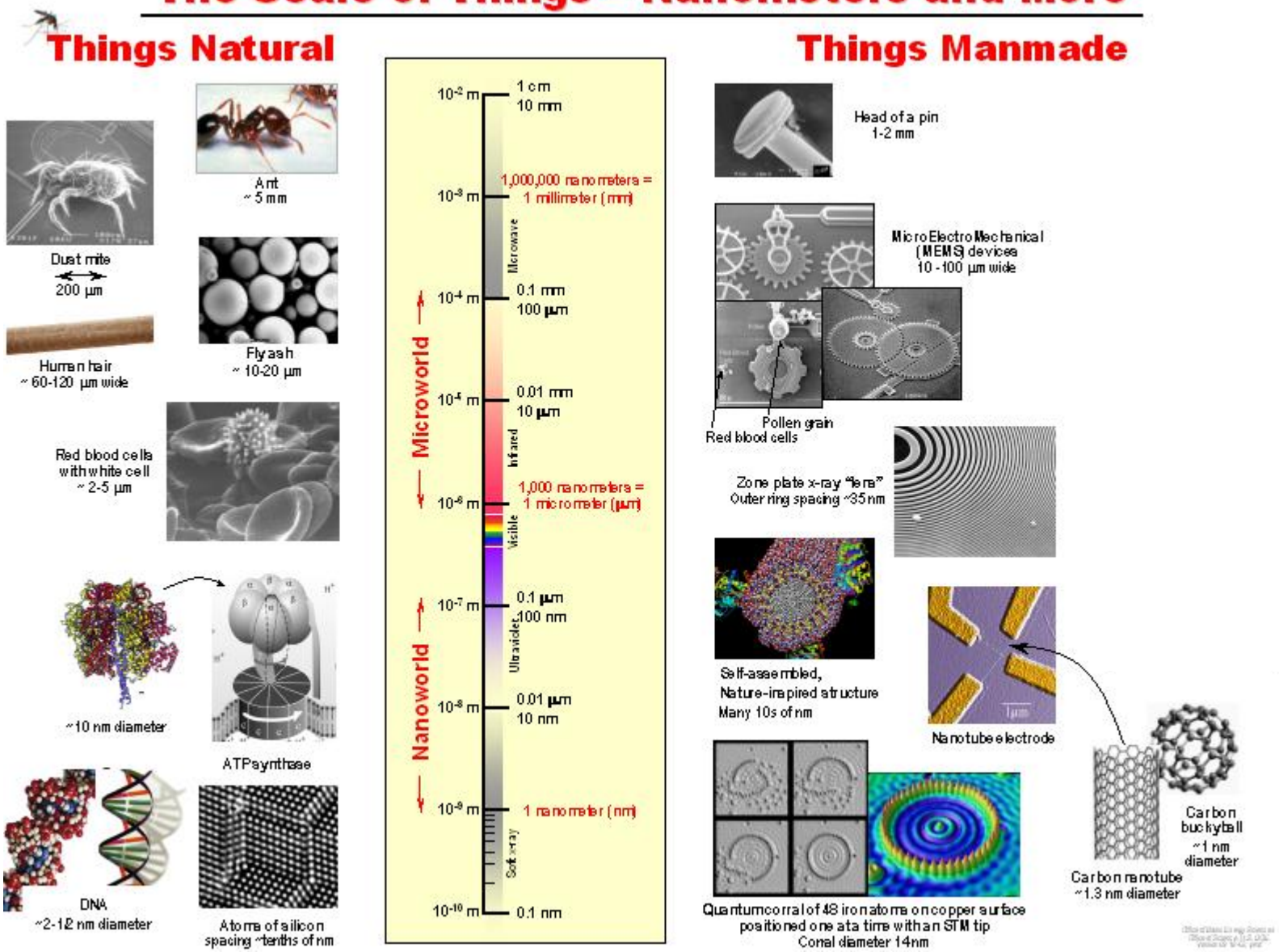
The Scale of Things – Nanometers and More



Courtesy Office of Basic Energy Sciences, Office of Science, U.S. Department of Energy

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Nanomedicine

- Whilst Life Scientists have been working at the nanoscale for many years (e.g. molecular biology), the **manufacture** of devices and materials at the nanoscale is an emerging and challenging area.
- Nanomaterials offer many **physical and chemical benefits** over conventional materials, for example, increased strength, solubility and reduced likelihood of immunorejection *in vivo.*
- Nanomedicine makes it possible to build technology on the same scale as human cells. This opens up incredible **new opportunities** for research and technological change in virtually every area of science.
- Whilst all of the above reasons support the growth of a nanomedicine industry, it is worthwhile pointing out at this stage that it is ***only an enabling technology, not a product*****.**

Key Nanomaterials

The building blocks of Nanomedicine fall into 4 main key material classes:

- Nanoparticles
- Fullerenes (“Buckyballs”)
- Carbon Nanotubes (CNTs)
- Dendrimers

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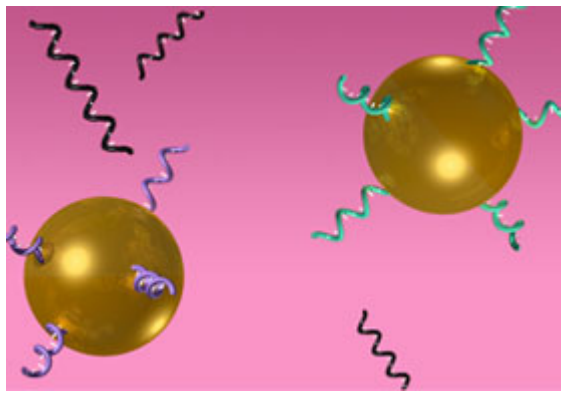
Nanoparticles

- 1-100nm in diameter.
- Traditionally synthesised from inert materials e.g. silver, gold and larger polymeric materials e.g. albumin.
- Can be used to generate nanoshells, containing a hollow core which can be filled with a variety of materials.
- Enhanced biological and chemical properties include, transport across cellular membranes, activated optical properties and controllable molecular aggregation



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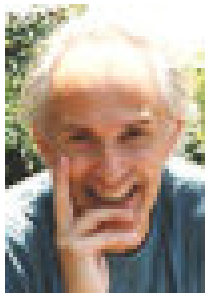
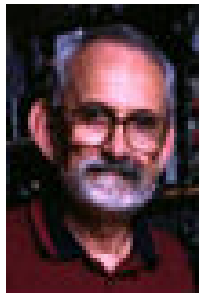
Fullerenes ("Buckyballs")

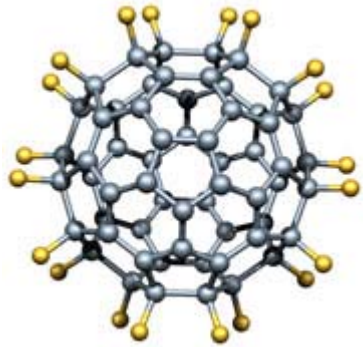


Sir Harold Kroto

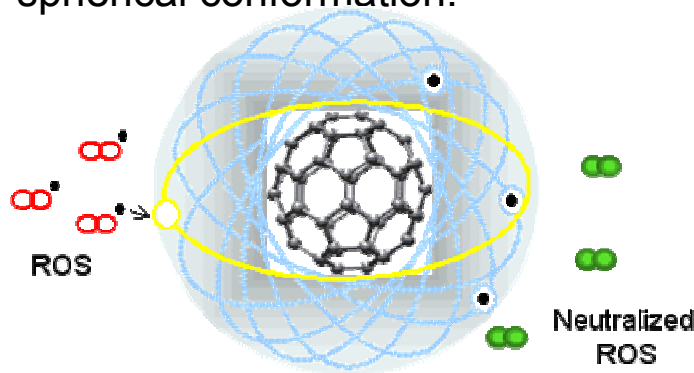
Richard Smalley



Robert F. Curl

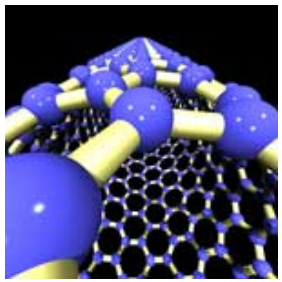


- Discovered in 1985 by Prof Kroto, Dr Smalley and Dr Curl Jr, who subsequently won the 1996 Nobel Prize for Chemistry for their discovery.
- ~1nm in diameter.
- Consist of a 60 Carbon structure (C60) arranged in a hollow spherical conformation.
- Inert but easily modified via the addition of chemical groups onto any of the carbon molecules.
- Possess powerful anti-oxidant properties.
- Buckyballs constructed from a specially prepared, branched DNA-polystyrene hybrid have recently been demonstrated.



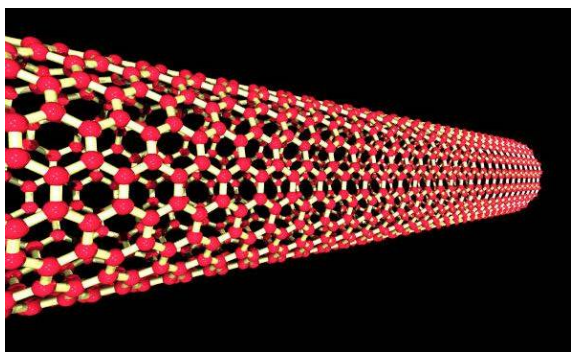
Fullerenes can capture multiple electrons derived from oxygen free radicals in unoccupied orbitals associated with its external electron cloud.

http://www.in-pharmatechnologist.com/news/news-ng.asp?n=62142-buckyballs-cornell-nanotechnology



Carbon Nanotubes (CNTs)

- Derived from Fullerenes in 1991 by Dr Iijima at NEC Corp.
- Consist of an extended hollow tube-like structure comprised of hexagonal graphite molecules.
- Can be joined together to form a series of nested, multiwalled concentric circles.
- Properties include, increased strength (100 times stronger than steel at one sixth of the weight).



Dr. Sumio Iijima

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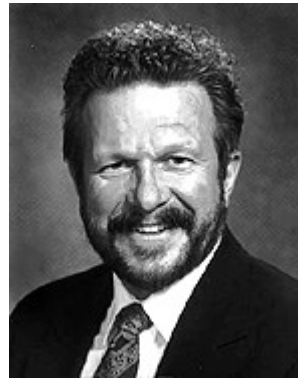
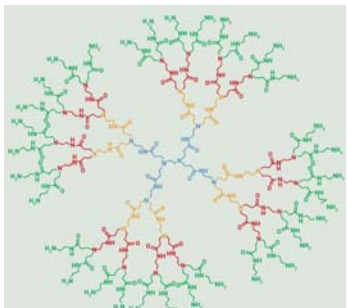
Dendrimers



Dr. Donald Tomalia

- Discovered in 1979 by Dr Tomalia and co-workers at Dow Chemical in Michigan
- Unique class of polymeric synthetic nanostructures.
- Consists of a polyfunctional core which reacts with additional branched monomers, which in turn possess end groups that can react with further groups.
- Classified via a generation system with the higher the generation, the increased number of functional branches.
- Properties include: rapid transport across biological membranes; increased solubility and increased loading capacity.
- Can be generated using a genuine “bottom up” approach by assembling the structures one atom at a time – mimicking the biological process, allowing near complete control of molecular size, shape, atom positions and disposition of reactive chemical groups (hence low immunogenicity).



Example of a third generation dendrimer.
The core is shown in blue and each successive generation is shown in a different color

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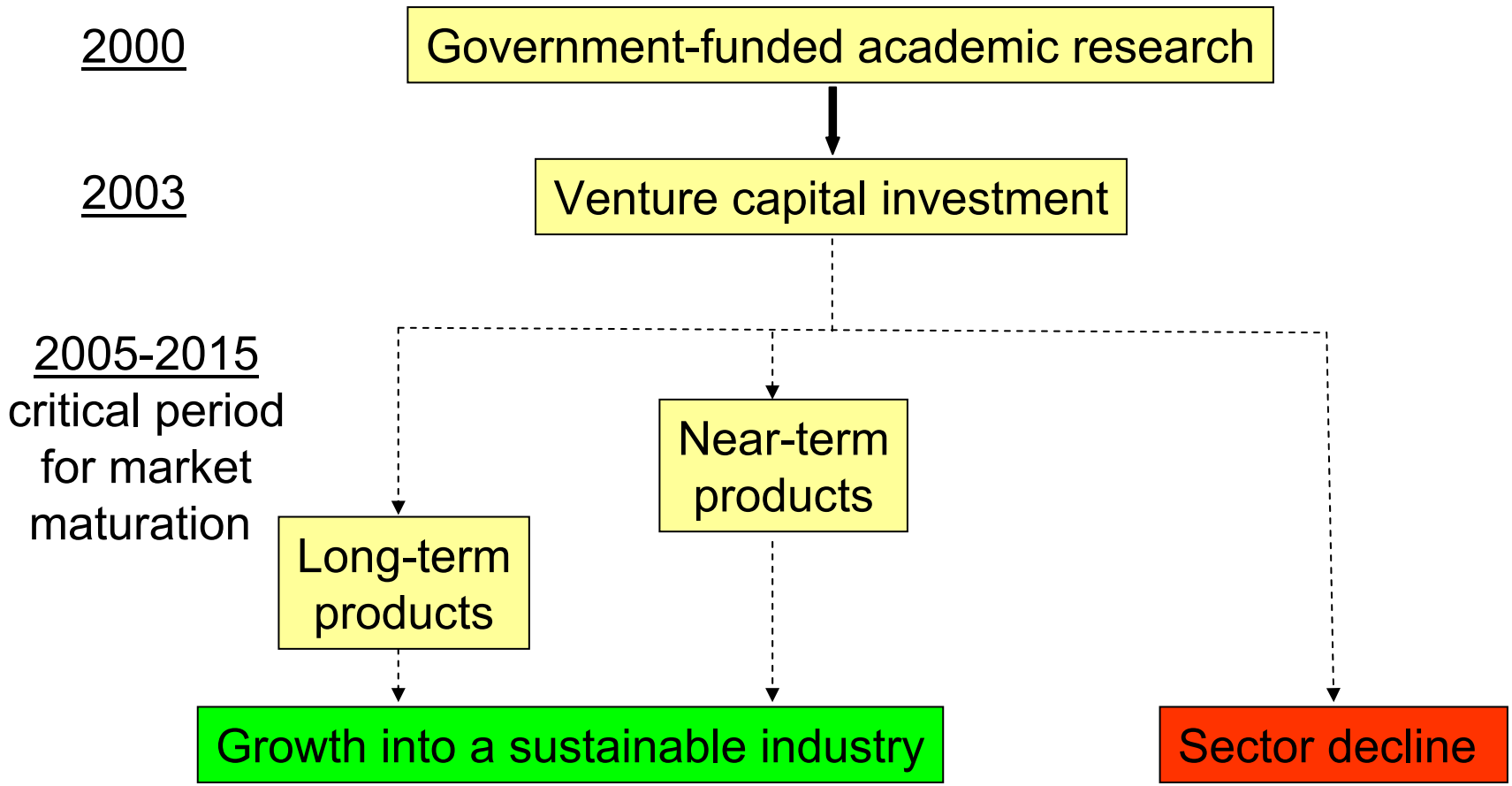

- Following considerable Government funding, the nanomedicine area has recently attracted a wave of entrepreneurship and VC funding.
- Full market maturation and sustainability relies upon the fulfilment of the promise that nanomedicine will deliver both short-term incremental improvement products and/or longer term novel products to the market place within the next 10-20 years to avoid the “boom or bust” scenario that blighted the dot-com industry.

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Nanomedicine Market Assessment

- At the present time, we believe there are **no approved *novel* nanomedicine products** on the market.
- The current approved nanomedicine-related products rely upon **incremental improvements** upon existing products, primarily utilising **size reduction strategies** to improve **drug reformulations.**
- This entails that at present, the nanomedicine market is primarily composed of the sales of nanomaterial **building blocks** and products mentioned above that improve the **lifecycle management** of current products.
- Longer term benefits of nanomedicine allowing novel functionalities, treatments and therapeutic regimens are still at the research phase and the market for these products is currently a **virtual one**.

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Marketed products that utilise nano-derived processes

Product	Sector	Material	Disease Indication	Technology Summary	Company
Abraxane	Drug delivery	Nanoparticle	Breast cancer	Albumin nanoparticles	American Pharmaceutical Partners
Rapamune	Drug delivery	Nanoemulsion	Immuno-suppressant	Nanocrystals (Elan)	Wyeth
Emend	Drug delivery	Nanoemulsion	Chemotherapy-induced nausea & vomiting	Nanocrystals (Elan)	Merck
Estrasorb	Therapeutic	Nanoemulsion	Estrogen replacement therapy	Oil and water nanoemulsion	Novavax Inc.
Silcryst	Wound care	Nanoparticle	Topical burn treatment	Silver nanocrystal particles	Nucryst

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Compounds in clinical trials that utilise nano-derived processes

Product	Sector	Material	Disease Indication	Development Stage	Company
NB-001	Therapeutic	Nanoemulsion	Herpes labialis	PII	Nanobio Corp
Basulin	Drug delivery	Nanoemulsion	Type I diabetes	PII	Flamel
Vivagel	Therapeutic	Dendrimer	AIDS	PI	Starpharma
Androsorb	Therapeutic	Nanoemulsion	Low testosterone in women	PI	Novavax
NB-004	Therapeutic	Nanoemulsion	Genital herpes	PI	Nanobio Corp
NB-005	Therapeutic	Nanoemulsion	Herpes zoster	PI	Nanobio Corp
IFNα-2b XL	Drug delivery	Nanoemulsion	Renal cancer	PI	Flamel
IL-2 XL	Drug delivery	Nanoemulsion	Hepatitis B and C	PI	Flamel
NB-002	Therapeutic	Nanoemulsion	Onychomycosis	PI	Nanobio Corp

- Clearly, the use of nanoprocesses for **size reduction** and **reformulation** strategies provide products and candidates that offer obvious improvements over current strategies. These include:
  - Improved **dissolution rates** of poorly soluble pharmacophores
  - Improved **bioavailability**
  - Reduced **toxicology**-related side effects
- By reformulating existing therapies, manufacturers also improve the products lifecycle management by:
  - Extending **patent protection**
  - Protect from generic competition
  - Optimise **revenue** generation
- By including these products, other analysts have suggested current annual nanomedicine revenues of up $750 million (includes sales of launched products and nanomaterial building blocks).
- In our opinion, however, the **real advantage of nanomedicine will only be fully realised when products that offer true novelty are approved.**

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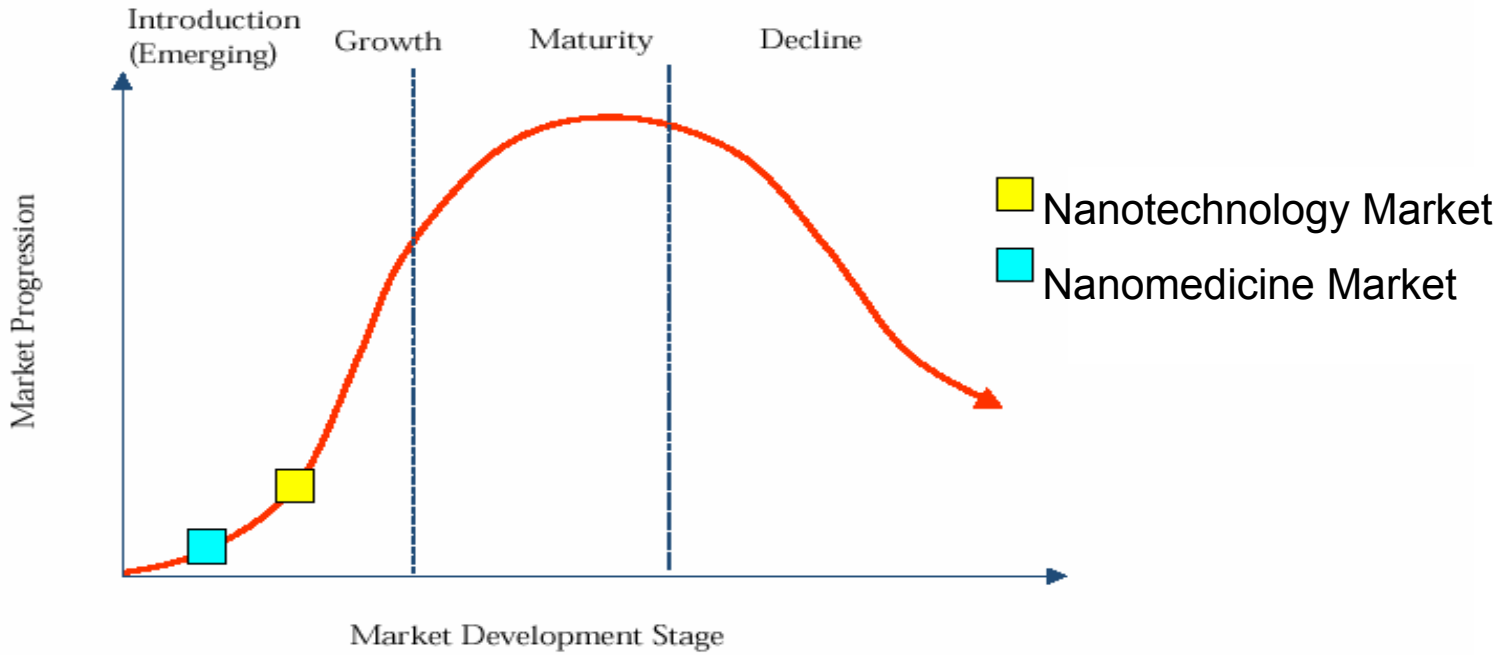
Current Market Status



- Nanomedicine is an **emerging market** with a **few approved products** utilising nanoderived processes offering **incremental improvements** upon existing products.
- There are currently no truly novel nanomedicine products on the market and as such the market could also be described as being a **virtual market** at the present time.
- It is less developed than the larger and more **mature nanotechnology** market, due to the successful implementation of novel nanotechnology products into the digital communications and electronics markets.
- The nanomedicine market is expected to develop as additional **short and long term products** mature and progress from the R&D phase into clinical trials and beyond.

Market data from Frost & Sullivan

Barriers and Opportunities for the Emergence of a Nanomedicine Market

- The ability and capability of nanomedicine products to reach the market place is affected by multiple parameters.
- The following section describes these **Market Barriers** and **Market Opportunities.**

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Nanomedicine Market – Barriers and Opportunities

Materials and manufacturing costs

Lack of Big Pharma Investment

Hype

Standardisation / Regulatory Affairs

Potential Safety Concerns

Miniaturisation of Existing Technologies

First products on Market

Strong Government and VC Investment

Innovative Solutions

Extended Drug Lifetimes

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Materials and Manufacturing Costs

- Material costs high.
- Low demand – fledgling industry. Presently only small (research) quantities being generated, leading to…
- Lack of large scale manufacturing facilities:
  - Large scale, high throughput, manufacturing technically difficult.
  - Time-demanding process e.g. a generation 10 dendrimer may take up to 6mths to manufacture.
  - Life sciences applications require very high purity synthesis.
  - Not feasible due to lack of commercial viability.
- Which in turn leads to elevated cost of small scale (lab-based) nanomaterials manufacture.
- Over time, increased use of nanomaterials through commercialisation will likely drive the manufacture to an increased scale and alleviate the above restraints.
- At present time however, this remains the biggest challenge facing the nanomedicine sector when compared to competing technologies.

- Multinational media hype over potential benefits of nanomaterials versus potential safety concerns. For example:
  - Sensationalist journalism.
  - News items about potential “breakthrough technologies”.
  - Blockbuster novels featuring nanotechnology, for example, Prey by Michael Crichton.
- Large amounts of funding, in turn, draw huge amounts of public expectation, which have at least, thus far, not been met by an equal number of nanomedicine products on the market.
- Variations in definitions as to what constitutes a nanomedicine product and hence variations in predicted market potential.
- All of which leads to a certain public opinion that more is expected from the nanomedicine sector that can actually be delivered.

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Potential Safety Concerns (1)

- Due to their small size, nanomaterials have different properties to conventional ones, giving them their unique advantage, but at the same time this may also bestow upon them some negative attributes which need to be identified:
  - Nanoparticles have novel drug metabolism and pharmacokinetic properties (DMPK) compared to standard compounds, hence standard metabolic routes may not be utilised. This raises the concern of potential persistence and bioaccumulation of nanomaterials within the body.
  - Uptake into cells depends upon particle size and coating type, hence biodistribution will vary amongst nanomaterials.
  - Potential biodegradability of toxic heavy metals from nanoparticles via the hepatic route of metabolism – need to ensure non toxic degradation path.
  - Potential blood-brain-barrier permeability issues and CNS toxicity e.g. one type of Fullerene was shown to cause brain damage in fish (Southern Methodist University, Dallas, Texas).

Potential Safety Concerns (2)

- All of the above ensure that additional, long term safety studies need to be carried out on any nanomaterial to demonstrate they do not have deleterious effects.
- Additional challenges from non-Government organisations e.g. Greenpeace, opposing the release of nanomedicines due to a lack of understanding concerning their potential effects on human health, therefore raises the bar with respect to obtaining consensus public approval. The industry needs to avoid inciting negative opinions and initiating another GM crop-like debate

Potential Safety Concerns (3)

- Safety implications of using such nanotechnology must be investigated within the earliest possible timeframe
  - Minimise any deleterious interactions between the physical materials and devices developed and biological tissues present in the manipulated tissue.
  - One potential way of achieving the safest possible technology is to design particles, devices or materials that are based on natural systems and can therefore be used *in vivo* without causing damage.
    - E.g Diamondoids have no heavy metals, are easy to synthesise, purify and analyse, have great diversity, a molecular weight of <500Da so may be orally administered, and have rigid structures, which increase bioavailability (www.moleculardiamond.com). May be useful in drug delivery, scaffolds, labelling agents and implantable devices.

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Potential Safety Concerns (4)

- Safety bodies empowered to investigate the safety implications of Nanomedicine:
  - **International Council on Nanotechnology (ICON),** established at Rice University's Center for Biological and Environmental Nanotechnology, which is conducting comprehensive safety studies for the FDA.
  - **SnIRC (Safety of Nanomaterials Interdisciplinary Research Centre).** Collaboration between:
    - Institute of Occupational Medicine, Edinburgh
    - University of Edinburgh
    - University of Aberdeen
    - Napier University
    - NIOSH (National Institute for Occupational Safety and Health, US)

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Standardisation / Regulatory Affairs

Currently neither the FDA, nor EMEA, have any specific regulations or standards surrounding the manufacture or use of nanomedicine for (pre)clinical safety assessment and are adopting a business as usual approach.

- Current opinion is that any new invention will be treated according to the therapeutic goal on a case by case basis and not by providing specific nanomedicine regulations.
- "Most drugs act as individual molecules that also are in the nanosize range, so nanomaterials are not new to FDA, and we have already dealt with it in many ways." said Nakissa Sadrieh, Associate Director for Research Policy and Implementation at the FDA.
- Primary focus is now on:
  - Introducing a standardised classification system for novel nanomaterials
  - Evaluating the potential safety / toxicological concerns using novel nanomaterials.

Regulatory Affairs – US

- FDA's Centre for Drug Evaluation and Regulation (CDER) currently analysing and developing new guidelines and models for establishing the potential effects of novel nanomaterials.
- Collaboration of the National Toxicology Program (NTP) and the International Union for Pure and Applied Chemistry (UK) is establishing new legislation and guidelines for the use of nanomaterials in human health.
- American National Standards Institute (ANSI) Nanotechnology Standards Panel met for the first time in Sept 2004 and are currently establishing clarity and continuity in nomenclature and classification of novel nanomaterials.

Regulatory Affairs - Europe

- Royal Society and the Royal Academy of Engineering published "Nanoscience and Nanotechnology: Opportunities and Uncertainties" in UK in Dec 2004.
- Similar surveys carried out in Germany and Switzerland.
- All of the reports point to similar conclusions:
  - Nanomaterials need to be classified as independent and novel classes of molecules and treated as such.
  - That a further standardised classification system should be implemented for nanomaterials.
  - Caution should be urged on the use of nanomaterials until appropriate safety research has been completed.
- With regards to appropriate classification, the British Standards Institution (BSI) has submitted a proposal to the International Organisation for Standardisation (ISO) for a novel field of classification for novel nanomaterials, that will include the establishment of new tests to assess the properties of the nanomaterials.

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Lack of Big Pharma Investment

- To date, primarily public and research council funding has driven the advancements in nanomedicine.
- Despite the advantages offered, funding and uptake from the private sector has been low:
  - E.g. the average Pharma investment in nanomaterials is <0.5% of their annual R&D budget, whereas the corresponding figure in the Electronics industry is 8%.
- Initial signs that this may be changing:
  - “Pfizer is currently trying to assess the current state of the art and promising avenues to develop a long-term strategy” Dr Analoui, Senior Director, Global Clinical Platform, Pfizer Global R&D when asked about Pfizer’s interest at a recent Nanotechnology conference.

- New industrial applications/artificial assemblies miniaturised to a previously inaccessible size.
- Allows the analysis of the physical, chemical & biological properties of molecules and structures inside living cells with similar quantum mechanical properties of atomic interactions.
- Nanomaterials offer many physical and chemical benefits over conventional materials:
  - For example, increased strength, solubility and reduced likelihood of immunorejection *in vivo.*

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Strong Government and VC Investment

- Huge Government investment into both nanotechnology and nanomedicine areas over the past 5 years.
  - Close to $1billion/yr invested in nanotechnology in US, Japan and Europe in 2004.
- Follow on VC funding becoming more apparent.
- Investment has led to huge advances in current understanding, primarily at the academic level.
- Initial signs of products utilising nano-derived processes making their way onto the market.

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- Blockbuster drugs approaching patent expiry can have their periods of exclusivity extended via the use of alternative formulations and delivery methods.
- Nano-derived processes can provide benefits such as new formulations with improved drug metabolism and pharmacokinetic properties over existing formulations.
- Long-term nanomedicine products will provide novel materials with which to produce new therapeutic and imaging agents.

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Innovative Solutions

- Great promise to provide solutions to medical problems that were previously unmet
  - Site-specific targeted drug delivery, minimising adverse effects on off target tissues.
  - Sensing and *in vivo* reporting of chemical imbalances within the body.
  - Improved tissue reconstruction, transplants and sensory aids.

Innovative Solutions (2)

- Multiple areas of impact:
  - Continuing the global trend of **miniaturisation**, allowing synthetic interactions at the atomic/molecular level, which were previously unattainable.
  - Improved **drug delivery** using lower amounts of drug, delivered precisely to the site where it is required, reducing potential toxicological side effects.
  - Improved in vivo sensing, **imaging** and visualisation of current disease states.
  - Improved **tissue reconstruction/regeneration** and reduced immunorejection of transplanted materials.
  - Lower weight materials with improved mechanical **strength** compared to those currently used.
  - Improved, smaller **sensory aids** to help improve visual and auditory impairments.
  - Advanced **surgical aids** increasing the precision, safety and accuracy of invasive surgical procedures.

Innovative Solutions (3)

- Many scientific breakthroughs have occurred at the convergence of individual disciplines.
- Nanomedicine fosters partnerships and the formation of multi- and inter-disciplinary teams consisting of, but not limited to:
  - Physicists
  - Chemists
  - Cell biologists
  - Molecular biologists
  - Physicians
  - Biomedical scientists
  - Biochemists
  - Engineers
  - Mathematicians
  - Computer scientists
  - Statisticians

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First Products onto the Market

The initial nanotechnology- and medical products utilising nano-derived size reduction strategies have recently been launched and are beginning to generate revenues. For example:

- TiO_2 nanoparticles **in sunscreen** which improve absorption and thus effectiveness
  - Photostable UV absorber with enhanced UVA protection and reduced free radical generation
  - Allows increased time between reapplications
- **Nanoparticle-based drug reformulations**, Abraxane
  - Minimises hypersensitivity reactions
  - Reduces infusion times

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Nanomedicine Applications and Examples

1. Diagnostic Genetic Testing
2. Imaging
3. Drug Delivery & Therapeutics
4. Implants, Scaffolds & Tissue Repair/ Regeneration
5. Sensory Aids
6. Surgical Aids

1. Diagnostic Genetic Testing

- *In vitro* analysis of gene sequences and expression levels are critical indicators of growth, metabolism, development, behaviour and adaptation of living systems.
- Nano- and micro-technologies may provide new solutions for **increasing the speed and accuracy** of identifying genes and genetic materials for drug discovery and development, and for treatment-linked disease diagnostics products.
- The market for in vitro diagnostic systems was around **$22 billion in 2003** (18% of the total medical devices market) with a **9% annual growth rate** and it could be expected that advances in nanomedicine would impact strongly upon this expanding market.

1.1 Ultra-sensitive Labelling and Detection Technologies

- New technologies are being developed to improve the ability to label and detect unknown target genes:
  1. GeniconRLS™ System for ultra-sensitive DNA microarray detection.
  2. Nanosphere's Verigene™ platform.
  3. Quantum dot (Qdot®) particles.

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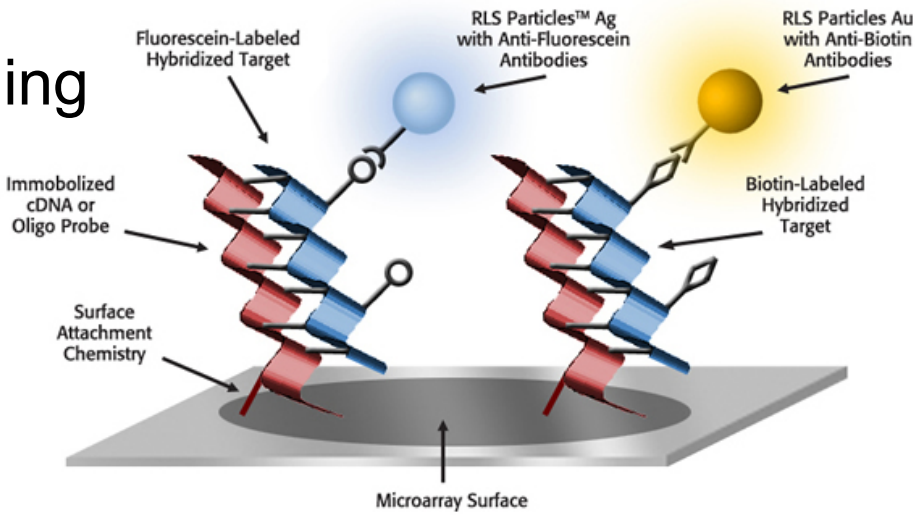
1.1.1 GeniconRLS™ System

- Genicon (now part of Invitrogen).
- Nanometer-sized gold particles that generate intense, monochromatic, scattered light signals upon white light illumination.
- Functionalized with anti-biotin and anti-fluorescein antibodies.
- Can be used in cDNA labelling and hybridisation studies.
- Achieve 10-fold greater sensitivity than with currently used CyDyes™.

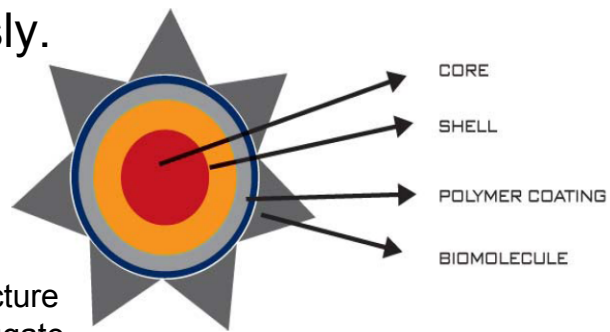


1.1.2 Nanosphere's Verigene™ platform

- Utilises gold nanoparticle probes coated with a string of nucleotides that complement one end of a target sequence in the sample.
- Another set of nucleotides, complementing the other end, is attached to a surface between two electrodes.
- If the target sequence is present, it anchors the nanoprobes to the surface.
- When treated with a silver solution, they create a bridge between the electrodes and produce a current.

1.1.3 Quantum dot (Qdot®) particles

- Qdot nanoparticles are composed of:
  - A core of cadmium sulfide (CdS), selenide (CdSe), or telluride (CdTe) encased by an insulating shell.
  - This is further encased by an outer layer composed of a hydrophobic/philic polymer with carboxylic acid derivatisation.
- Coating allows attachment of biological and non-biological moieties e.g. antibodies, streptavidin, lectins, nucleic acids.
- Qdots emit light brightly in a range of sharp colours and can be used to label and detect biological targets.
- Colours can be tailored by changing the size of the dot, hence multiple biological molecules can be tracked simultaneously.
- Do not fade when exposed to ultraviolet light.
- Stability of fluorescence allows longer periods of observation.



Schematic of the overall structure of a Qdot® Nanocrystal conjugate

Advantages of Aforementioned Technologies

- All of the described technologies:
  - Are more sensitive than currently used fluorescent dyes.
  - Can effectively detect low abundance and low-level expressing genes.
  - Use smaller and less expensive equipment to detect the samples.
  - Do not require gene amplification, hence results are generated in less time.

1.2 High Throughput Arrays and Multiple Analyses

- With continued miniaturisation, possibilities exist to greatly increase the number of spots on a single substrate array chip.
- Entire genome on a single chip ?
- Using nanomaterials as sensing particles and nanofluidic technologies, chips should also decrease in size.
- Smaller and more portable integrated diagnostic kits for systemic lupus or other multi-marker diseases.
- Micro/nano-fluidic devices in the form of nanoarrays, or lab on a chip technologies, could allow the production of smaller, more portable more efficient and disposable DNA and protein sequencers for drug discovery and diagnostic kits.

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2. Imaging

- "For diagnostics and molecular imaging, we can now get anatomical, organ-level information. For the future, we want cell and molecular-level information. That's where nanomedicine comes into play". Dr Kulkarni (GE Global Research Centre).
- Nanomedicine is creating new imaging technologies that represent vast improvements in both image quality and specificity of the target.
- These fall into 3 main categories:
  - **Nanoparticle Probes.**
  - **Miniature Imaging Devices.**
  - **Implantable Devices**.
- The market for imaging systems and agents is large, for example in 2004:
  - Medical imaging systems represented $18 billion (8% of the total medical devices market).
  - Imaging tools and agents (including contrast media and radiopharmaceuticals) represented $5 billion
  - Tools for molecular preclinical and clinical imaging represented $1 billion
  - Patient monitoring represented $1.9 billion

2.1 Nanoparticle Probes

Example 1. University of Michigan.

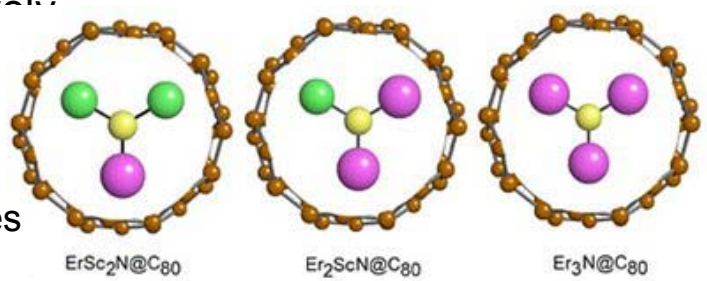
Developing nanoparticles with a magnetic core, attached to a cancer antibody that adheres to cancer cells. The particles are also linked to a contrast agent which is visible using magnetic resonance imaging (MRI). Allows the imaging of cancer cells and their subsequent destruction by laser heating

Example 2. University of Washington.

Nanoparticles, with attached probes and therapeutics, are being used to bind specifically to proteins emitted from newly formed capillaries delivering blood to solid tumours. Once attached, chemotherapeutics are released into the capillary membrane and destroy the tumor. The nanoparticles travelling in the bloodstream would be able to locate additional cancer sites which may have spread to other parts of the body.

Example 3. Luna Innovations

Developing newly discovered nanomaterials called Trimetaspheres™. Hollow molecules of carbon atoms enclosing various metal and rare earth elements, including gadolinium. Used to enhance traditional MRI images by up to 50 times. If successful, could result in the use of lower magnetic fields through smaller, cheaper and portable imaging equipment. Alternatively, smaller amounts of contrast agents could be used which would reduce the risk of allergic reaction in some patients.



Examples of Trimetaspheres™ Species

2.2 Miniature Imaging Devices

Example 1. Given Imaging

- Developed a pill containing a miniature video system. Once swallowed, it moves through the digestive system and takes pictures every few seconds. Can be utilized to diagnose diseases of the small intestine including Crohn's Disease, Celiac disease and other malabsorption disorders, benign and malignant tumors of the small intestine, vascular disorders and medication related small bowel injury

Example 2. MediRad

- Developing a miniature x-ray device that can be inserted into the body. Attempting to make carbon nanotubes into a needle shape cathode. The cathode would generate electron emissions to create extremely small x-ray doses directly at a target area without damaging surrounding normal tissue

2.3 Implantable Devices

- Nanotechnology can offer new implantable and/or wearable sensing technologies that provide **continuous** and extremely accurate medical information
- Complementary microprocessors and miniature devices can be incorporated along with sensors to **diagnose** disease, **transmit information** and administer treatment automatically if required
- **Real-time monitoring** of the body's systems could facilitate the detection of undesirable conditions and effects far earlier than is currently possible
- This will provide a far more detailed model of the body's systems and processes, which will help doctors predict the effects of various diseases and treatments. Diagnosis will become far easier and more informative
- Implantable devices fall into 2 categories:

  2.3.1 **Implantable Sensors**

  – Sensors capable of monitoring and detecting changes in a local environment.

  2.3.2 **Implantable Medical Devices**

  – Devices capable of both sensing changes in a local environment and adapting to the changes by e.g. administering drugs, eliciting an electrical charge or a mechanical output.

2.3.1 Implantable Sensors

Example 1. University of Michigan

- Transdermally administered, fluorescently tagged dendrimers. Sense pre-malignant and cancerous changes inside living white blood cells. Tags glow in the presence of the dying cells when passed with a scanning device using a laser capable of detecting the fluorescence.
- NASA developing similar application for detecting radiation levels in astronauts

A computer model of a dendrimer, carrying methotrezate (red), folic acid (purple) and fluoresceine (green), used to track the dendrimer in the bloodstream.

Example 2. Texas A&M and Penn State

- Monitoring blood sugar levels in diabetes patients using polyethylene glycol beads coated with fluorescent molecules. Beads are subcutaneously injected and when glucose levels drop to dangerous levels, glucose displaces the fluorescent molecules and creates a glow which is visualised on a tattoo placed on the arm.

2.3.2 Implantable Medical Devices

Example 1

- Site specific application of chemotherapeutics to exact sites of tumour cell growth could be achieved, on demand, using electrically stimulated microfluidic systems, miniature pumps, and reservoirs. Lupus, diabetes and HIV/AIDS applications are also being investigated.

Example 2.

- Microprocessor-regulated implantable sensors and defibrillators could be used to monitor the heart's activity level and to deliver electrical currents, ensuring that the heart is kept in rhythm.

Example 3.

- An artificial leg being developed uses sensors to measure load on the foot, knee angles and motion over 50 times per second. The sensors work with an electronically controlled hydraulic knee to improve its stability.

Example 4. University of Aalborg.

- Using nanostructures to activate denervated muscles caused by injuries to the lower motor neurons located in the spinal cord. The muscle fibre membrane is incorporated with potential-generating nanostructures that change the transmembrane potential of the muscle fibre and improves the extracellular electrical stimulation. Muscle fibre activation is achieved by illuminating the incorporation site on the muscle fibre to optically activate denervated muscles

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3. Drug Delivery & Therapeutics

Critical formulation attributes for efficient drug delivery:

- Protect drug from body. Avoid premature drug degradation / metabolisation prior to it reaching intended site of action.
- Protect body from drug. Minimise potential adverse effects of the drug on organs other than the target organ.
- Ability to cross necessary barriers required to reach target e.g. blood-brain barrier.
- Rate at which the drug is released at its site of action.
- Drug delivery material that meets all of the above criteria, must be compatible and bind easily with the drug, be bioresorbable and be cost efficient to manufacture.

Advantages Nanomedicine can bring to Drug Delivery / Therapeutics

- Drug delivery (reformulation of an existing drug, on the market using a different formulation)
- Therapeutics (compounds / treatments in development, not currently on the market
  - Increased efficacy
    - Improved drug uptake.
    - Improved specificity of drug delivery.
  - Increased safety
    - Reduced toxicological side effects.
    - Less drug used
- The worldwide market for advanced drug delivery systems is estimated to be around $54 billion. Half of this market is in controlled-release systems, with needle-less injection, injectable/implantable polymer systems, transmucosal, rectal, liposomal drug delivery and cell/gene therapy responsible for the rest.

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Mechanisms whereby nanomedicine may aid drug delivery

3.1 Drug Encapsulation.

- By forming a protective layer around the active drug, the capsule protects both the drug from the body and vice versa.

3.2 Functional Drug Carriers.

- Certain nanostructures can be controlled by linkage to a drug, a targeting molecule, and/or an imaging agent. This allows the carrier to attract specific cells and/or release their payload at the specific site where the drug is most required, hence minimising potential adverse toxicity.

3.3 Nanoemulsions

- Milling of a drug to nanometre particle size to improve drug metabolism and pharmacokinetic properties

3.1 Encapsulation

Nanomedicine allows:

- Controlled timed release of the drug through pores or diffusion of the drug during capsule degradation.
- Formation of nanocapsules provide:
  - a larger surface area for the same volume.
  - smaller pore size.
  - improved solubility.
  - different structural properties.
- Leads to improved diffusion and degradation of the encapsulation material.
- Improved transport across body compartments.

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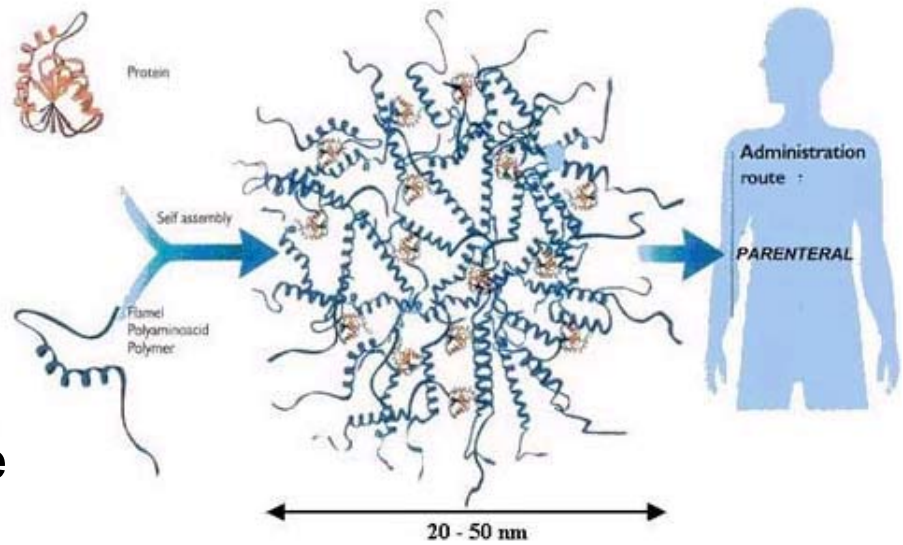
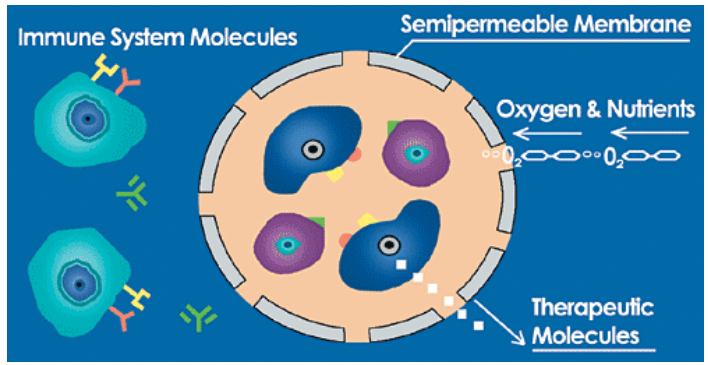
3.1.1 Encapsulation

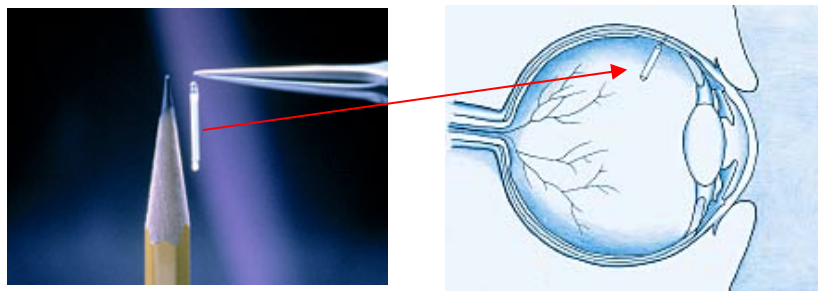
- Example 1. Flamel Technologies Inc.
- Developed the Medusa encapsulation platform.
- Comprised of a poly-amino acid nanoparticulate delivery system.
- Five therapeutics using the system are currently being developed in house:
  - Basulin for the treatment of type I diabetes (Phase II).
  - IL-2 XL for the treatment of renal cancer (PhaseI/II).
  - IFNα-2b XL for the treatment of hepatitis B and C (PhaseI/II).
  - EPO XL for the treatment of anemia (Preclinical).
  - hGH XL for the treatment of growth hormone deficiency (Preclinical).



3.1.2 Encapsulation

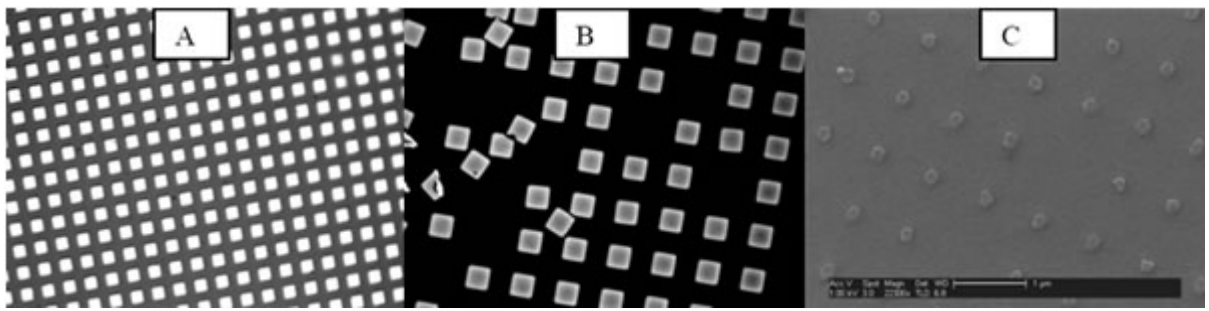


- Example 2. Neurotech.
- Encapsulated cell therapy to treat eye diseases.
- Semi-permeable membrane encapsulates cells, permitting therapeutic agents produced by the cells to diffuse through the membrane.
- Membrane isolates the cells from the local environment and minimizes immune rejection.
- Administered by a device implanted in the eye to permit the continuous release of therapeutic molecules from living cells.



3.1.3 Encapsulation

- Example 3. Liquidia Technologies Inc.
- Designed the world's smallest manufactured particles for delivering drugs and biological materials.
- The technology, Particle Replication In Nonwetting Templates (**PRINT**™), enables fabrication of custom-sized, monodispersed and shape-specific particles of virtually any material and encapsulating nearly any active cargo.
- Rolland et al. (2005) J. Am. Chem. Soc.

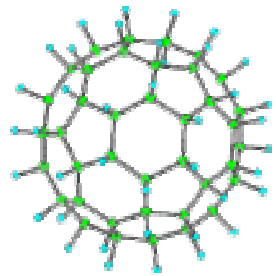


Directly fabricated or printed micro- and nano-scale particles made using "PRINT™"

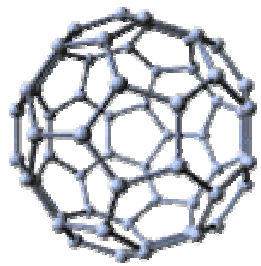
3.2.1 Functional Drug Carriers

- Example 1: **Abraxane** – Abraxis / American Pharmaceutical Partners
- First nanoparticulate drug delivery product was launched 8th February 2005.
- Abraxane (paclitaxel), an albumin nanoparticle associated protein drug for the treatment of metastatic breast cancer was launched by Abraxis Oncology, a division of American Pharmaceutical Partners, Inc.
- Allows the drug to access parts of the body that were previously inaccessible to other formulations.
- Eliminates potential side effects as albumin does not provoke an immune response.

3.2.2 Functional Drug Carriers



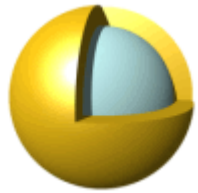
- Example 2: **Fullerenes (or Buckyballs)** – C Sixty Inc.
- Drug delivery platform allowing
  - Active pharmacopheres to be grafted to its surface in 3-D orientations for precise control in matching fullerene compounds to biological targets.
  - Entrapment of atoms within the fullerene cage.
  - Attachment of fullerene derivatives to targeting agents.
- C Sixty Inc. is developing:
  - Fullerene-decorated chemotherapeutic constructs.
  - Fullerene-radiopharmaceuticals.
  - Fullerene-based liposome systems (Buckysomes), for the delivery of single drug loads or multiple drug cocktails.
- Technology currently being developed for delivery of HIV/AIDS, neurodegenerative disorders and cancer drug candidates.



3.2.3 Functional Drug Carriers

- Example 3: **Dendrimers**
- Polymer molecule discovered by Don Tomalia of Dendritic Nanotechnologies
- Small size and branched structure, allows compounds to be attached and released in response to a specific molecule or chemical reaction.
- University of Michigan are using dendrimers to get genetic material or tumour-destroying therapies into a cell without triggering an immune response.
- StarPharma is developing VivaGel™, a water-based gel that contains the polyvalent, polylysine dendrimer, SPL7013, as the active ingredient. SPL7013 has shown activity against multiple viral sexually transmitted diseases.
- Nanoparticle clusters of two different functional dendrimers, one for imaging and the other for targeting cancer cells recently announced. Verification that the dendrimers hit their targets, were admitted into the cells, and gave off their signalling light was provided.

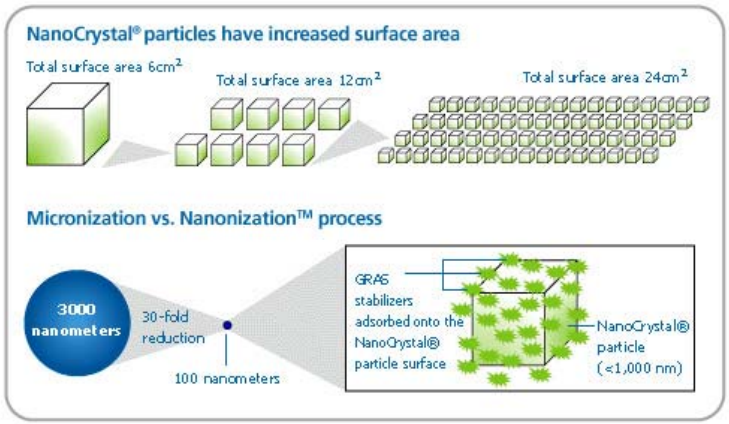
3.2.4 Functional Drug Carriers



- Example 4: **Nanoshell** – Nanospectra
- Layered sphere for drug delivery.
- Technology licensed from Rice University Centre for Biological and Environmental Nanotechnology (CBEN).
- Gold exterior layer covering interior layers of silica and drugs.
- Can be made to absorb light energy and convert it to heat, thus destroying neighbouring cells.
- When placed next to a target area such as a tumour cell, it can release tumour-specific antibodies when infrared light is administered.
- Initiating clinical trials for the treatment of mesthelioma in mid-2006.

3.3 Nanoemulsions

- The market leader in nanoemulsions is Elan Pharmaceuticals Inc.
- Developed a nano-crystallisation system for milling drug compounds to nanometre scale particles, improving surface area to volume ratios
- Benefits include improved biological uptake into patients.
- Already successfully applied to:
  - Wyeth Pharmaceuticals Inc. Rapamune for use in immunosupression during transplant surgery.
  - Merck & Co., Inc. Emend for control of chemotherapy induced nausea and vomiting.
- Technology is currently being used by Roche and Johnson&Johnson (reformulating paliperidone palmitate for use in a Phase III clinical trial for Schizophrenia).



4. Implants, Scaffolds & Tissue Repair/Replacement

- Few types of medical device are implanted permanently.
- Limited functionality can be incorporated into a device small enough to fit inside the body.
- Surgery remains traumatic unless minimally invasive procedures are possible.
- Nanomedicine devices:
  - Will be far more efficient and compact than those that exist today.
  - As technologies mature, implantable devices will be able to continuously sense and adjust the body's chemical balance.

4.1 Implant Coatings

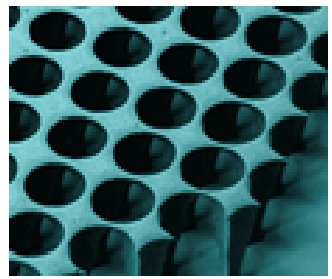
- Previously used biocompatible micro-sized implant coatings can be made into nano-sized particles to increase their surface area to volume ratio and improve their adhesion properties.
- Maximum possible contact area between the implants and, for example, the bone surface to improve the potential for in-growth in the host bone.
- Novel nanomaterials are also being evaluated as implant coatings, for example:
  - polyvinyl alcohol (PVA) to coat implantable devices that are in contact with blood (e.g. artificial hearts, vascular grafts, catheters) for dispersing clots or preventing their formation.

4.2 Scaffolds

- Develop molecularly-sensitive nanopolymers.
- Manipulate the **rigidity and strength** of scaffolds using hybrid nanostructures.
- Preparation of **nanosurfaces** to maximize **long-term viability** and function of cells on scaffold surfaces.
- Study the fundamental properties of implanted tissues, using tracers to image implanted cells *in vivo*.
- Study the response of the host to implanted tissues.
- Biggest challenge - molecular/cell biology and **fabrication methods** for producing large 3D scaffolds.
- **Example. Vitoss/Cortoss** – Orthovita.
  - Vitoss is a calcium phosphate nano-scaffold which has been approved for market in the US, Australia and Europe. The primary applications are in spinal surgery and in the repair of osteoporotic fractures.
  - Cortoss, a similar scaffold has been designed to mimic human cortical bone and is available in Europe.

4.3 Bone repair

- Novel nano-compatible materials could be used for bone repair and cavity fillers.
- Can be made into flowable, mouldable nanoparticle pastes.
- Interdigitate with bone.
- Biocompatibility should be extremely high with minimal side effects.
- Suitable for both weight bearing and non-weight bearing bones.
- Nanocrystalline structure allows formation of connective hard tissue suitable for nutrient transport.
- **Example 1. NanOss** - Angstrom Medica Inc.
  - Synthetic bone manufacture using calcium and phosphate nanoparticles to produce a nanocystalline structure, NanOss.
  - Mimics the synthesis of natural bone and can be used in bone grafts and as a replacement structure to minimise the necessity for allografts.
- **Example 2. BioSilicon** – PSiVida / Qinetiq.
  - BioSilicon is a nanostructured porous silicon with potential as an artificial bone scaffold.
  - Shown to stimulate the growth of osteoblasts and promote bone mineralisation.
  - Could potentially be used as an orthopaedic coating.



4.4 Bioresorbable Materials

- Example 1. Nanostructured implants
  - Designed to degrade at a rate that will slowly transfer load to a healing bone that it is supporting.
- Example 2. Flexible nanofibre membrane meshes
  - Can be applied to heart tissue in open-heart surgery.
  - Can be infused with antibiotics, painkillers and medicines and directly applied to internal tissues.
  - Will degrade over time and not stick to surgeons' wet gloves.

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5. Sensory Aids

- Nano-technologies are being used to develop a new generation of smaller and potentially more powerful devices to restore lost vision and hearing functions.
- The devices collect and transform data into precise electrical signals that are delivered directly to the human nervous system.

5.1 Retinal Implants

- Retinal degeneration can progress to diminishing peripheral vision and blindness due to a progressive loss of photoreceptors
- In cases where the neural wiring from the eye to the brain is still intact but the eyes' lack photoreceptor activity, photoreceptor loss could be compensated by bridging or bypassing the destroyed photoreceptors and artificially stimulating the adjacent intact cells.
- Artificially generated impulses could reach the brain and produce visual perception, thereby restoring some elementary vision.

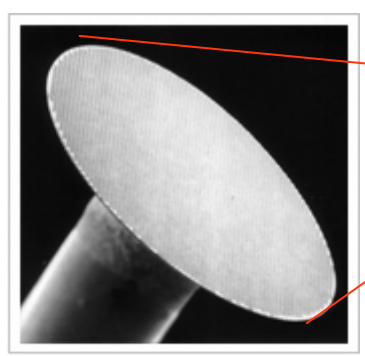
5.1 Retinal Implants

Example 1. Argonne National Laboratory.

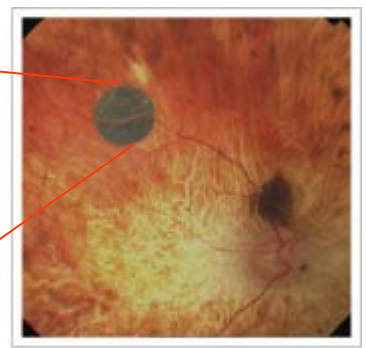
- Artificial retina implanted in the back of the retina.
- Uses a miniature video camera attached to a visually-impaired person's eyeglasses to capture visual signals.
- The signals are processed by a microcomputer worn on the belt and transmitted to an array of nanoelectrodes placed in the eye.
- The array stimulates optical nerves, which then carry a signal to the brain.

Example 2. Optobionics.

- Artificial Silicon Retina (ASR)™ microchip is designed to stimulate damaged retinal cells
- The visual system is activated when the membrane potential of overlying neurons is altered by current generated by the implant in response to light stimulation.
- The implant makes use of a microelectrode array powered by as many as 3,500 microscopic solar cells.



Magnified image of an ASR® device



ASR® device implanted in the human eye

5.2 Cochlear Implants

- Current cochlear implants have a number of drawbacks:
  - Require major surgery.
  - Can eliminate any remaining natural hearing.
  - Because of their large size, often stimulate several nerve fibres at once, leading to distorted sound.
- Next generation cochlear implants will consist of:
  - An implanted nanotransducer pressure-fitted onto the incus bone in the inner ear causes the bones to vibrate, stimulating the auditory nerve.
  - An array at the tip of the device using up to 128 electrodes (5x more than current devices), leading to greater clarity & precision.
  - The implant is connected to a microprocessor and a microphone (built into a wearable device that clips behind the ear).
  - This captures and translates sounds into electric pulses which are send down a connecting wire through a tiny hole made in the middle ear.

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6. Surgical Aids

- Invasive surgery is timely, dangerous and exhausting work
- Laparoscopic techniques are becoming more prevalent but still have disadvantages:
  - Shift in the skills required to master the equipment.
  - Reduced vision and access to the working site.
  - Working on a 2-D image on a video screen rather than the 3-D operating field.
- Nanotechnologies could be applied to aid surgery by **increasing the precision, safety and accuracy**, as well as performing new tasks that are not currently achievable.
- Example 1. Verimetra.
  - Developing an enhanced version of its Data Knife, incorporating embedded nanosensors. Provides surgeons with real-time information on:
    - Force and performance of their instruments.
    - Tissue type about to be cut.
    - Specific tissue properties, such as density, temperature, pressure, and electrical impulses.
- Nanoparticles also being investigated for optically guiding surgery.
  - Potentially allow for better removal of lesioned or diseased sites, including tumours.

Nanomedicine market potential

- As mentioned, assessment of both the current market size and future market potential depends upon the **definition** of nanomedicine utilised.
- Using the strictest definition, the market for nanomedicine is a **virtual** one, since at the present time, it is primarily an **enabling technology**, with **no truly novel products currently approved**.
- However, if the products on the market that make use of nano-derived processes to provide **incremental improvements to existing products** and the **nanomaterial building blocks** (nanoparticles, dendrimers, CNTs and fullerenes) themselves are included, a niche market does currently exist.
- This market currently lags well behind the larger and **more developed nanotechnology market**, examples of which are provided in Appendix 1.
- However, in our opinion, **the true value of nanomedicine will not be fully appreciated until these longer term, high value products, are at a more advanced stage of development**

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Funding

- The worldwide investment in **nanotechnology** research and development in 2004 from both public and private sectors was an estimated **$US8.4 billion**.
- An estimated 15% **($US1.25 billion**) of this was directed at **nanomedicine** applications.
- The nanomedicine sector only made up around 8% of the nanotechnology industry focus groups with regards to researchers worldwide in 2004 (Fig), hence relative funding per head is greater than other nanotech sectors.
- Funding in nanomedicine is plentiful and increasing but is still primarily Government and, to a lesser extent, VC-backed.

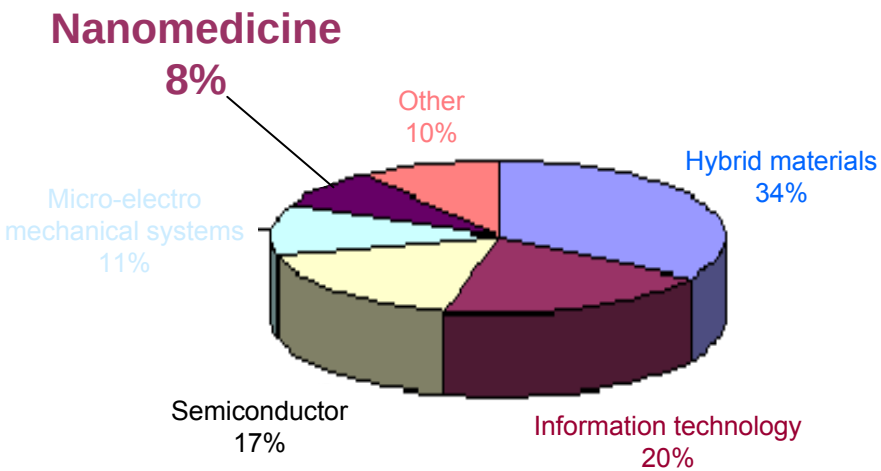

Figure: World nanotechnology industry focus in 2004 according to sector. Nanomedicine companies represent around 8% of the overall industry.

Market data from Frost & Sullivan

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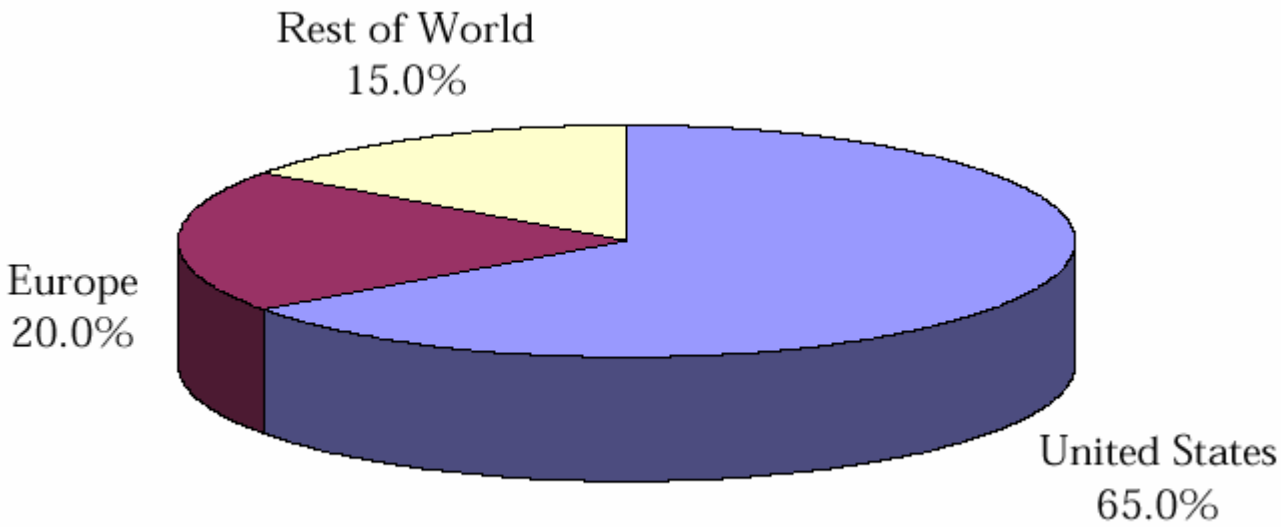
Geographical Distribution of Nanomedicine Investment

2004



- The US currently invests significantly more in Nanomedicine than any other country.
- This is potentially attributable to the significant Government funding available through the National Nanotechnology Initiative (NNI).

Market data from Frost & Sullivan

Nanomedicine Funding in North America

- The **National Nanotechnology Initiative** was unveiled by President Clinton in a speech in January 2000.
- Nanotechnology funding has increased year-by-year to $961million in 2004.
- In December 2004, a further $3.7billion over the next 4y was allocated for nanotechnology, with a **specific focus on nanomedicine**.
- Individual US states are also dedicating considerable funds to nanotechnology
  - Illinois awarded $17million to Argonne National Laboratories in 2003 for a Centre for Nanoscale Materials, to focus on nanocarbon technologies and bioinorganic interfaces.
- The National Cancer Institute (NCI) initiated a $144million, 5y alliance for nanomedicine in cancer.
- Further funding for Centres of Cancer Nanotechnology Excellence (CCNEs) will be made available in 2005 to enhance nanomedicine in drug delivery and cancer therapeutics

Nanomedicine Funding in North America

The NIH identified **nanomedicine** as one of its five initiatives included under the major Roadmap theme of "New Pathways to Discovery" for advancement of biomedical research in the next 10 years.

- Launch meeting was in May 2004.
- Goal of "*Initiating biologically motivated discovery and development that will incorporate nanotechnology tools, devices and processes to provide fundamental insights into cellular function and dysfunction, leading to therapeutic interventions for disease*".
- The initiative will invest $6 million for 3-4 Nanomedicine Development Centres (TBD September 2005) in the specific areas of:
  - Quantitative characterization of the physical and chemical properties of molecules and molecular assemblies in living cells
  - Study of the design principles of assemblies in living cells
  - Creation of tools and nanoscale components to function in cells for repairing damage and curing disease

Nanomedicine Funding in Asia/Pacific

- Whilst nanotechnology is now one of the main Science and Technology priority areas for Asia Pacific governments (>$1billion invested for the past 2 years), investment into the field of nanomedicine has been **slower than in the US**.
- Japan has initiated the Nanotechnology Research Institute (NRI) to be the main collaborative organisation, coordinating nanomedicine and nanotechnology research.

Nanomedicine Funding in Europe

- The European Commission will invest $570M on nanotechnology research in 2005 via FP6 grants, an **increase of 25%** over previous year.
- Proposals are in place to **double the budget for nanotechnology**, with **specific reference to nanomedicine**, in the next round of funding, FP7 (2006-2010).
- The **European Technology Platform on Nanomedicine** was launched at the EuroNanoForum meeting in Edinburgh on 6th September 2005.
- **Nano2life** was launched with $11million over 4y under Framework Protocol 6 (FP6) to encourage collaborations and networking between pan-European nanomedicine labs.
- The Pan-European Forum for Nanotechnology, **Nanoforum** was recently launched following a European-wide public consultation on nanotechnology in December 2004
  - Aims to promote and advance nanotechnology and nanomedicine in Europe.
  - Led by The Institute of Nanotechnology, (ION) UK but includes national nanotechnology organisations from Germany, France, Spain, Denmark and the Netherlands.
- The European Nanotechnology Trade Association (ENTA) was established by the ION to:
  - Act as a bridge between national and regional Governments and companies
  - Interface with the public and watchdog organisations.
  - Ensure that member organizations develop new nanotechnologies in a safe and responsible manner

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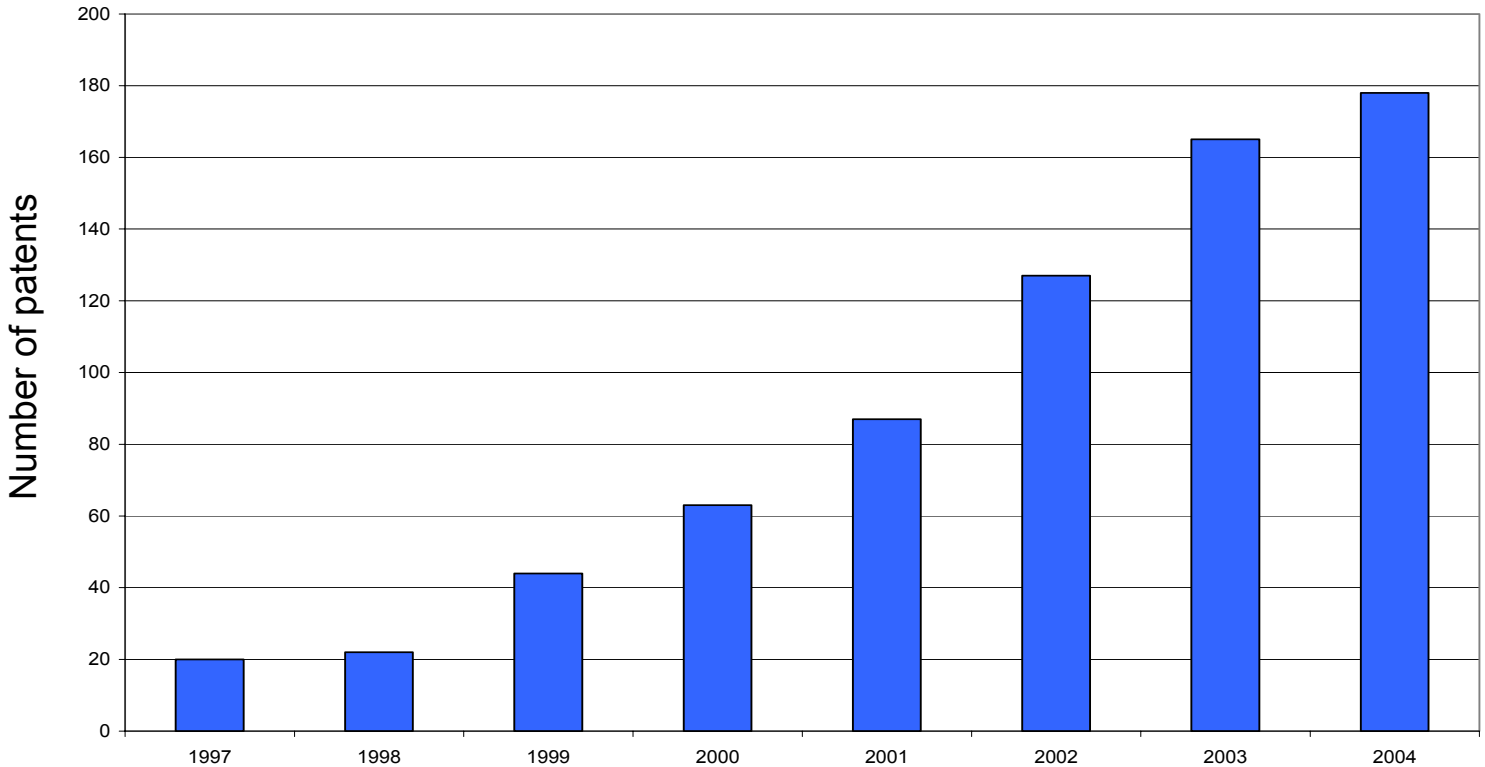
Increase in Nanomedicine Patenting Activity over Time



- This data excludes any patents pertaining to nanomaterial synthesis and refers only to those with direct medical applications
- Nanomedicine patenting activity has increased steadily since 1999

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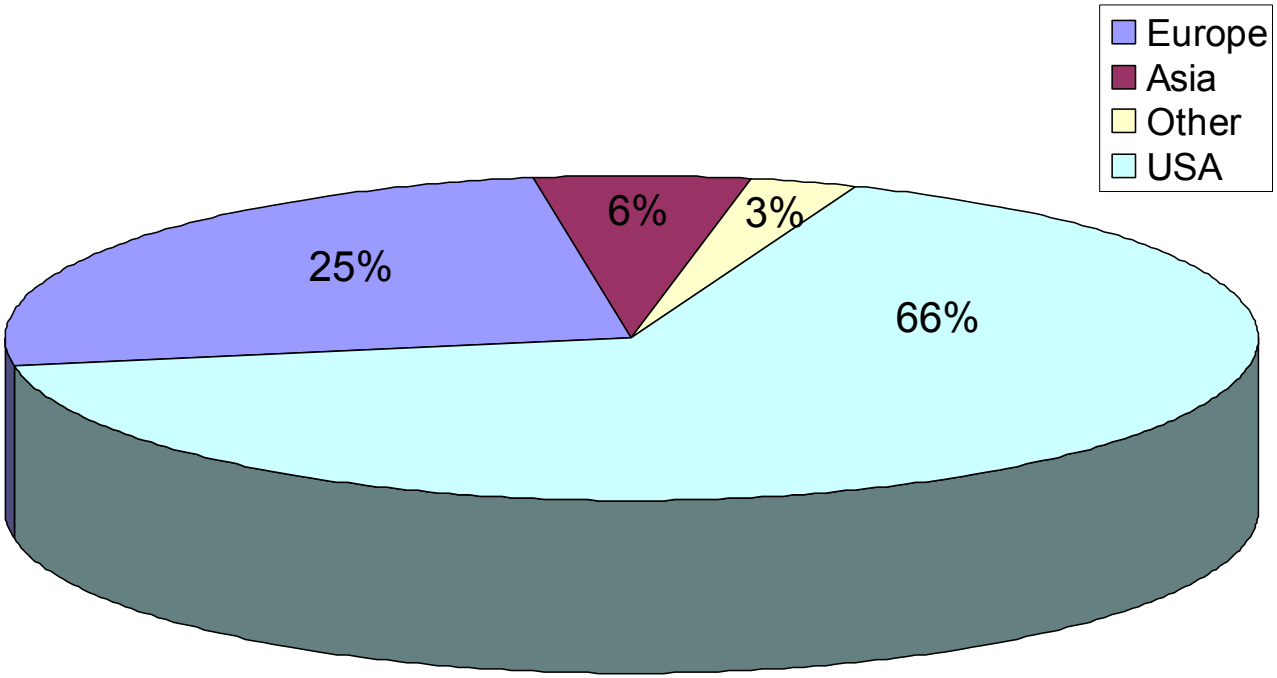
Priority Patent Applications Filed in Each Territory



- The US leads the way with respect to priority patent applications in the nanomedicine area.

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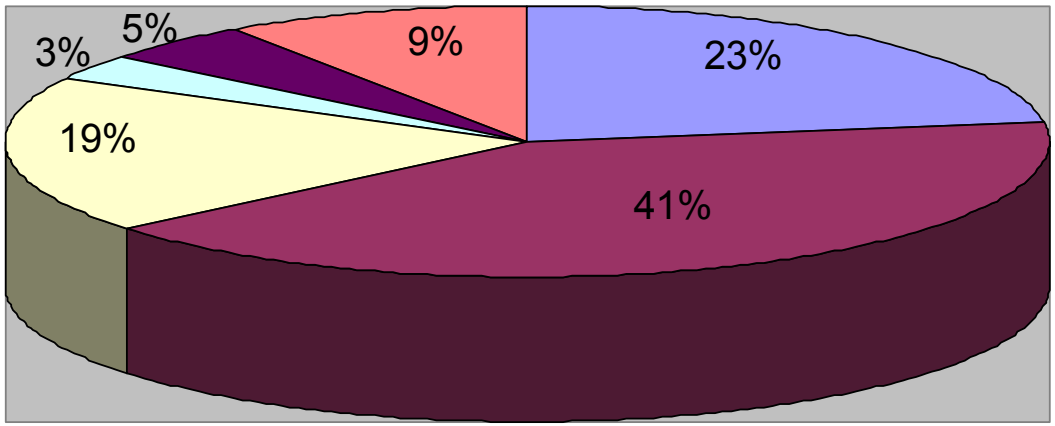
Overview of Patenting Activity in Defined Technical Categories



- Drug delivery; diagnostic genetic testing; and imaging and sensors make up >80% of all patenting activity in the nanomedicine area

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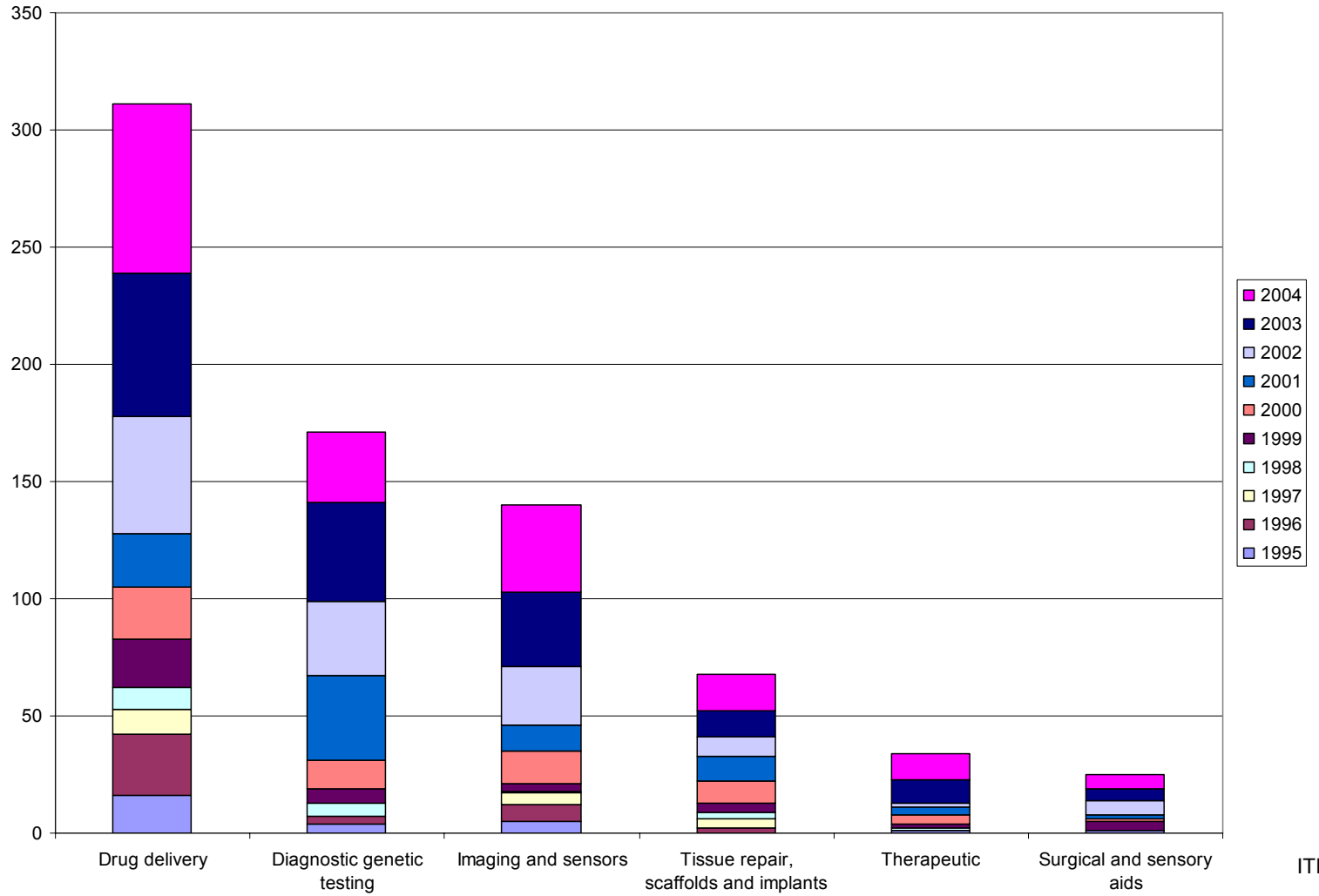
Overview of Patenting Activity in Defined Technical Categories Over Time



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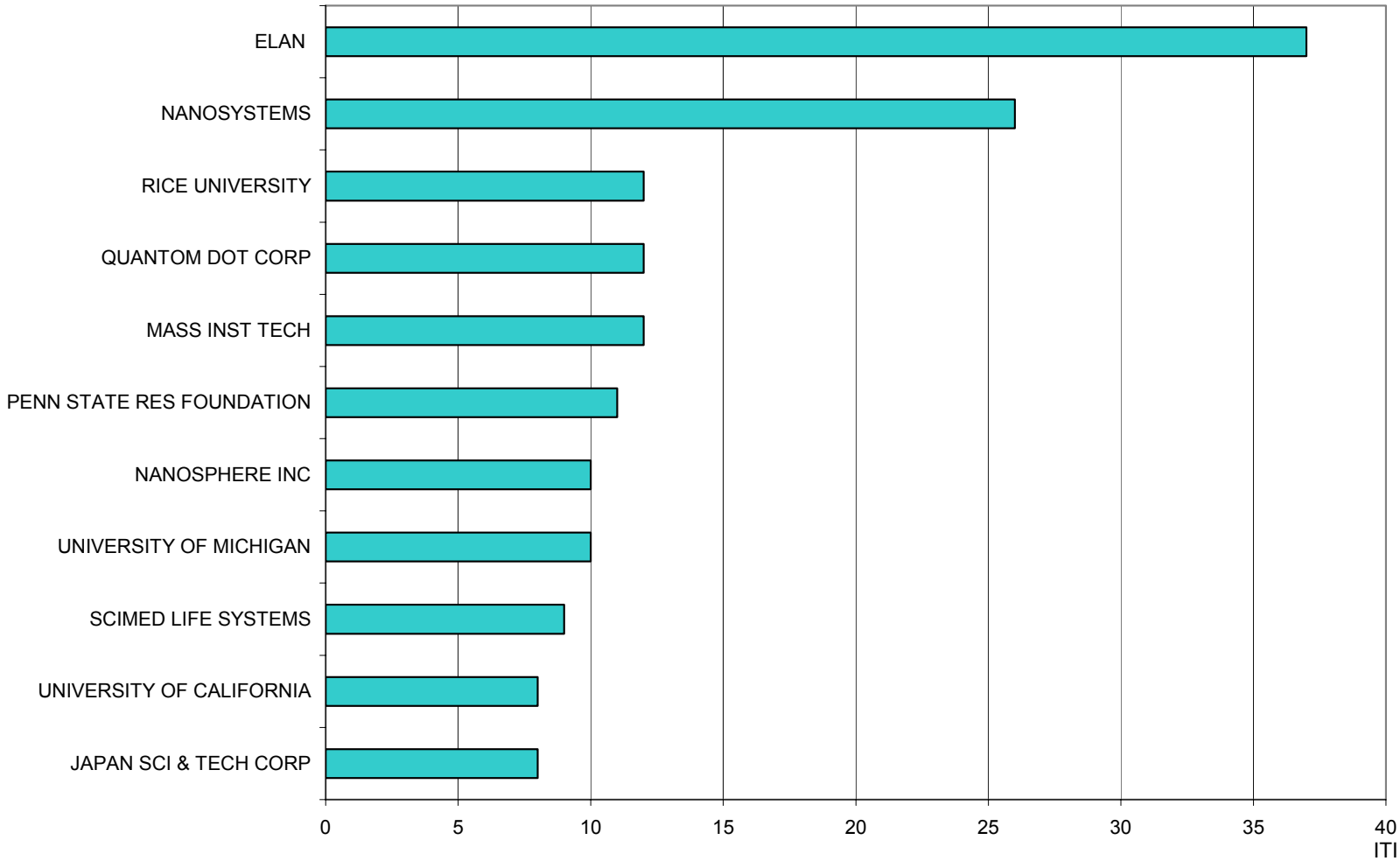
Organisations with Highest Levels of Patenting Activity in Nanomedicine



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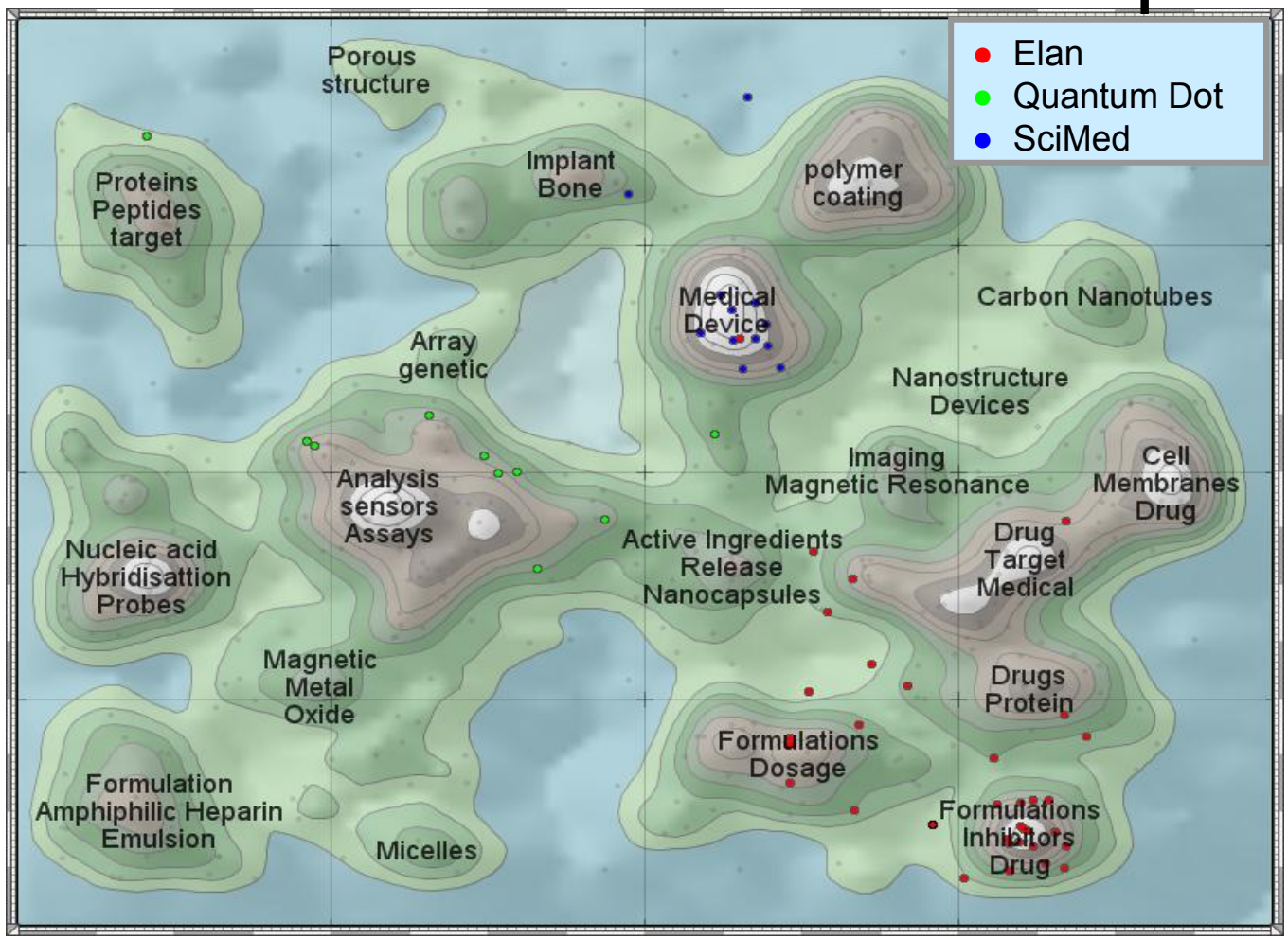
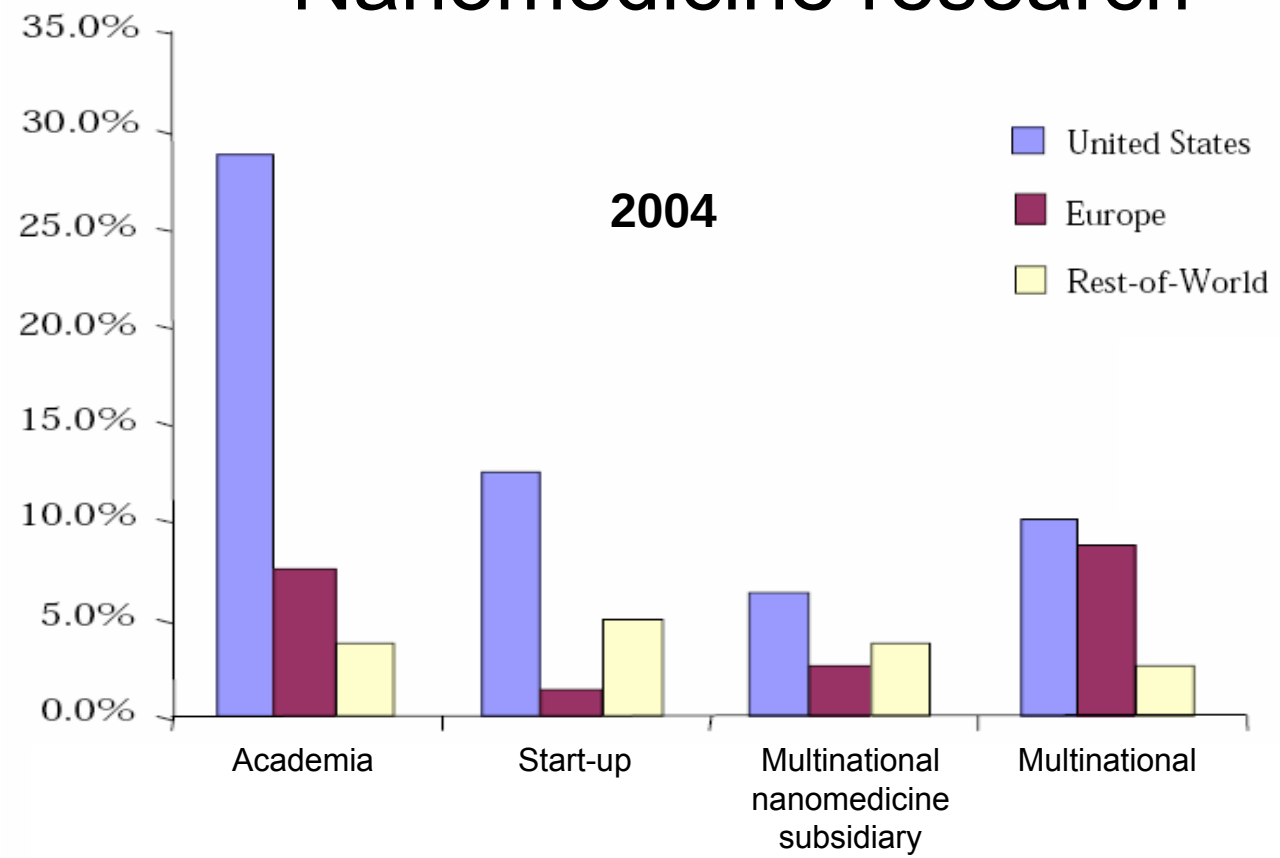
Nanomedicine Patent Map



Keywords within an identified set of patents and patent applications in the field of Nanomedicine are grouped into topics to produce a 'map'. Collections of documents which share common elements are geographically close together whilst collections with less similarity are further away. The patent landscape is therefore displayed as a series of technology 'mountain tops' and 'valleys' with the higher 'mountains' representing the larger patent collections. Specific key companies, Elan, Quantum Dot Corp and SciMed are identified on the map, demonstrating which fields of Nanomedicine they operate in.

ITI generated data

Types of organisation carrying out Nanomedicine research



- The vast majority of nanomedicine research is still at the academic research stage in the US, although there is a much more even spread across academia and the commercial sector in Europe and the Rest of the World.

Market data from Frost & Sullivan

Scottish Fit

- Strong research base in the area of nanotechnology, with several initiating multifunctional, crossover groups into the area of nanomedicine.
- Multiple, diverse academic labs, primarily working in the areas of nanomaterials, drug delivery, bionanosensors, genomic nanoprocessors, nanosurfaces and tissue engineering with the greatest concentration at the Universities of Glasgow, Strathclyde, Edinburgh and Dundee.
- Most work is carried out in relatively small groups with little or no industrial funding.
- Two nanomedicine-related companies, both involved in drug delivery, XstalBio and Nanomerics.
- Institute of Nanotechnology, Stirling
- Institute of Occupational Medicine, Edinburgh

Companies

- **Nanomerics**, Glasgow
  - Aims: Improve the delivery of small molecules and gene therapies with sub-optimal DMPK parameters
  - Management:
    - Dr Andreas Schatzlein, Beatson Laboratories, Univ. Glasgow
    - Prof Ijeoma Uchegbu, Dept Pharmaceutical Sciences, Univ. Strathclyde
    - David Gough, First Instar Ltd, formerly Avlar BioVentures and Vectura Ltd.
    - Bob Damms, formerly Merlin Biosciences, PA Consulting, ICI/Astra Zeneca
    - Mel Anderson, Research and Enterprise, Univ. Glasgow
  - Technology: Targeted polymeric nanoenvelopes to repackage drugs/genes to offer improved efficacy, safety and value.

- **XstalBio Limited**, Glasgow
  - Aims: To improve delivery of therapeutic proteins, peptides, DNA and vaccines
  - Management:
    - Dr Marie-Claire Parker (CEO)
    - Dr Barry D. Moore (CSO)
    - Dr Mike Billinham (Business Development)
  - Technology: Advanced drug delivery using protein-coated microcrystals

Institute of Nanotechnology

- Founded in 1994 by Ottilia Saxl (previously the Centre for Nanotechnology)
- Global leader in nanotechnology information provision.
- Fosters communications and collaborations between Governments, Universities, researchers, and companies worldwide.
- Serves as a key organizer of international scientific events, conferences, and educational courses.
- Is the key co-ordinator of the pan-European Nanoforum:
  - Europe's premier nanotechnology information network, fully funded by the EU.
- Organiser of the recently launched European Nanotechnology Trade Alliance (ENTA) which will:
  - Act as a bridge between national and regional Governments and companies
  - Interface with the public and watchdog organisations
  - Ensure that member organizations develop new nanotechnologies in a safe and responsible manner

Institute of Occupational Medicine

- Based in Edinburgh.
- The premier independent UK centre for research, consultancy and training in occupational and environmental health, hygiene and safety
- Provide research, reviews and risk assessments to assist clients in the formulation and implementation of policy and development of good practice.
- Has formed a multidisciplinary consortium, the Safety of Nano-materials Interdisciplinary Research Centre (SnIRC) Initiative to address nanoparticle risk issues.
  - Collaboration between internationally recognised researchers at the IOM and the Universities of Edinburgh, Aberdeen and Napier and the US National Institute of Occupational Safety and Health (NIOSH).

Conclusions (1)

- The analysis of the nanomedicine market is complicated by the fact that it is actually an **enabling technology, rather than a product** and also by a **definitions issue** of what actually constitutes a nanomedicine product
- We define two separate potential markets:
  - ***Short or near term goals*** which will bring **performance gains** for existing therapeutics / pharmaceuticals, as well as sales of existing nanomaterials.
  - ***Long term goals*** which will bring **novel and innovative solutions** to current unmet clinical requirements.
- ***Near term goals* (present to 5 years):**
  - Will be driven by **lifecycle improvements** to existing therapeutics, primarily via **drug delivery reformulations**, leading to optimising revenues, extending patent life and competition over generics
  - Will include benefits such as improved solubility profiles, increased bioavailability and reduced toxicological side effect profiles
- ***Long term goals (5-10 years plus)*:**
  - Will be driven by requirements for **new functionality, treatments and therapeutic regimens**, as well as **truly novel products to treat and diagnose currently unmet clinical requirements**.
  - Will offer benefits such as increased efficacy and **specificity of drug delivery** via targeted approaches; **convergent therapy** delivery combined with imaging; **real time in vivo monitoring** of the internal chemistry of the body; **early detection** of undesirable conditions; **improved safety, strength, viability of implants combined with reduced immunorejection.**

Conclusions (2)

- Due to the **lack of approved long term nanomedicine products** at the present time, this market is currently a **virtual** one
- The main trading commodities at the present time are the nanomaterials themselves:
  - **Nanoparticles**
  - **Fullerenes ("Buckyballs")**
  - **Carbon Nanotubes (CNTs)**
  - **Dendrimers**
- The global market for the sales of the nanomaterial building blocks, combined with the near term approved products that utilise nano-derived processes, can be estimated to have generated revenues of around $750million in 2004. If the R&D involved in the ongoing search for long term products continues, the nanomaterials market is likely to expand at a year on year CAGR of 15.5% over the next 6 years.
- Nanomedicine is therefore a **segmented**, but **emerging market**, which is less developed than the larger and more mature nanotechnology market.
- Most research is still taking place within the **academic** environment, although spin-out and start-up companies are becoming more abundant

Conclusions (3)

- High levels of **Government funding** are likely to **drive the potential nanomedicine market** in the short term, but additional opportunities include: initial interest from VC funding; the first near term nanomedicine products now being launched; the **promise of longer term innovative solutions to previously unmet medical needs**.
- The primary challenge to the emergence of a nanomedicine market is the **expense of nanomaterial manufacturing**. Additional barriers include: the **lack of safety / toxicology** information and the **lack of any standards and regulatory affairs** to deal with the pipeline of novel nanomedicine products.
- All of the above need to be addressed as soon as possible to encourage and enable further development of nanomedicine products. Once in place, the additional barrier of a **lack of serious Pharma backing and investment**, will also need to be addressed.
- Areas in which nanomedicine is forecast to have major benefits include:
  - **Diagnostic Genetic Testing**
  - **Imaging**
  - **Drug Delivery & Therapeutics**
  - **Implants, Scaffolds & Tissue Repair / Regeneration**
  - **Sensory Aids**
  - **Surgical Aids**

Appendices

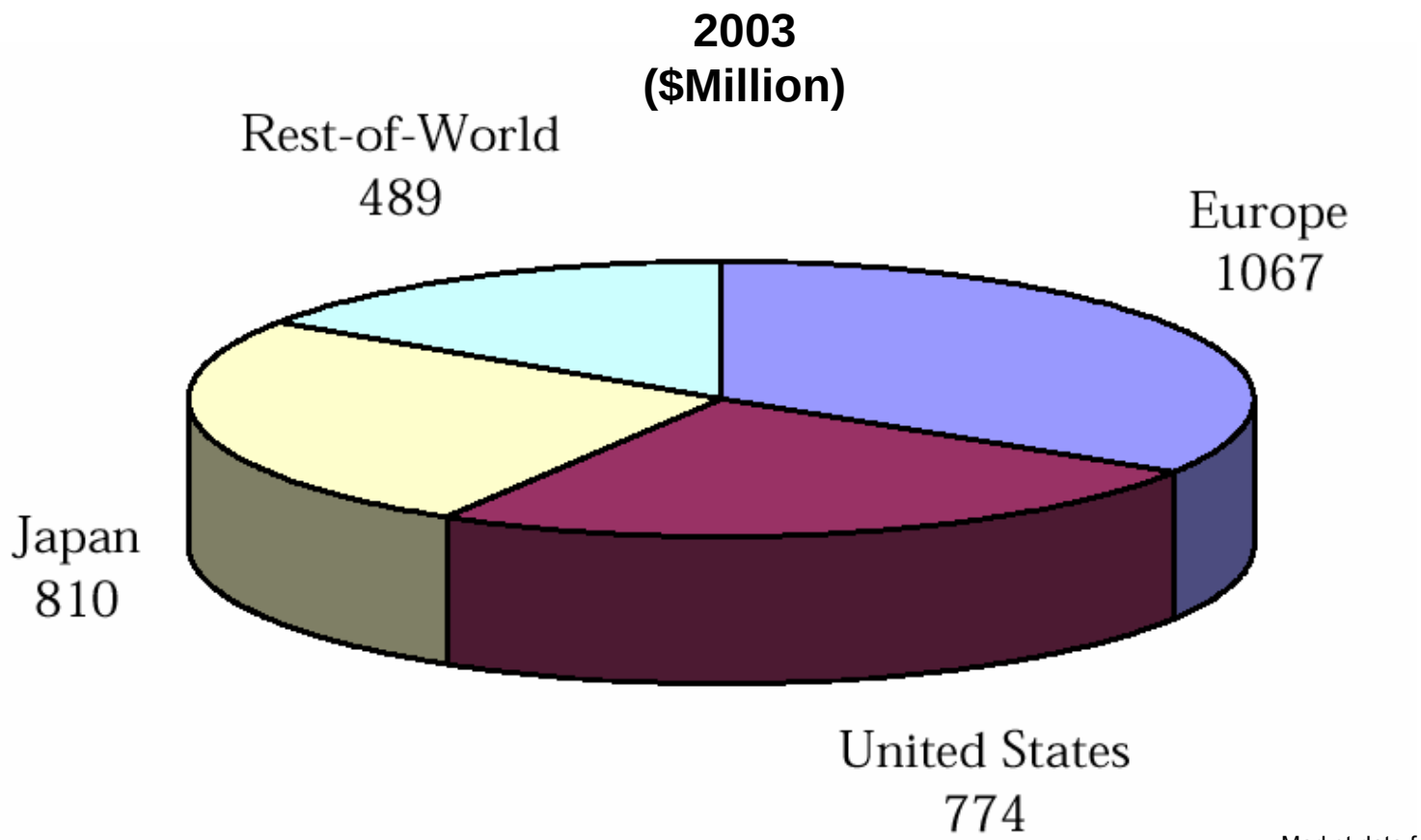
Nanotechnology – Multiple Major Impact Markets

- Communications
- Information storage
- Material sciences
- Medical

"In 10-15 years **$1 trillion** in products worldwide will be affected by nanotechnology. Almost everything related to advanced materials, medicine, pharmaceuticals, environment, energy conversion, and national security will be affected".

Dr Mihail Roco, Director, US National Nanotechnology Initiative

Government Nanotechnology Investment



Market data from Frost & Sullivan

Nanotechnology Funding in North America

- The National Nanotechnology Initiative was unveiled by President Clinton in a speech in January 2000.
- In its 2001 budget submission to Congress, the Clinton administration raised nanotechnology to the level of a federal initiative.
- Funding has increased year-by-year to $961 million in 2004.
- Establishment of 8 Nanoscale Science and Engineering Centres (NSEC) with a further 5 in development. Coordinated by the National Science Foundation (NSF).
- In December 2004, a further $3.7 billion over the next 4y was allocated for nanotechnology
- There are currently over 250 companies in the US involved in nanoscale R&D

Nanotechnology Funding in North America

- Significant nanotechnology effort underway in Canada.
- Strong support for R&D and a commitment from the various Provincial Governments.
- As well as the National Institute for Nanotechnology, there is also Nano-Quebec:
  - a nanotechnology initiative of the Government of Quebec
  - a nanotechnology laboratory within the Quebec National Institute for Scientific Research
  - Nano Innovation Platform under the Natural Sciences and Engineering Research Council (NSWRC).
- Canada's core nanotechnology research is in the laboratories of the National Research Council and the major Canadian research universities.

Nanotechnology in Asia / Pacific

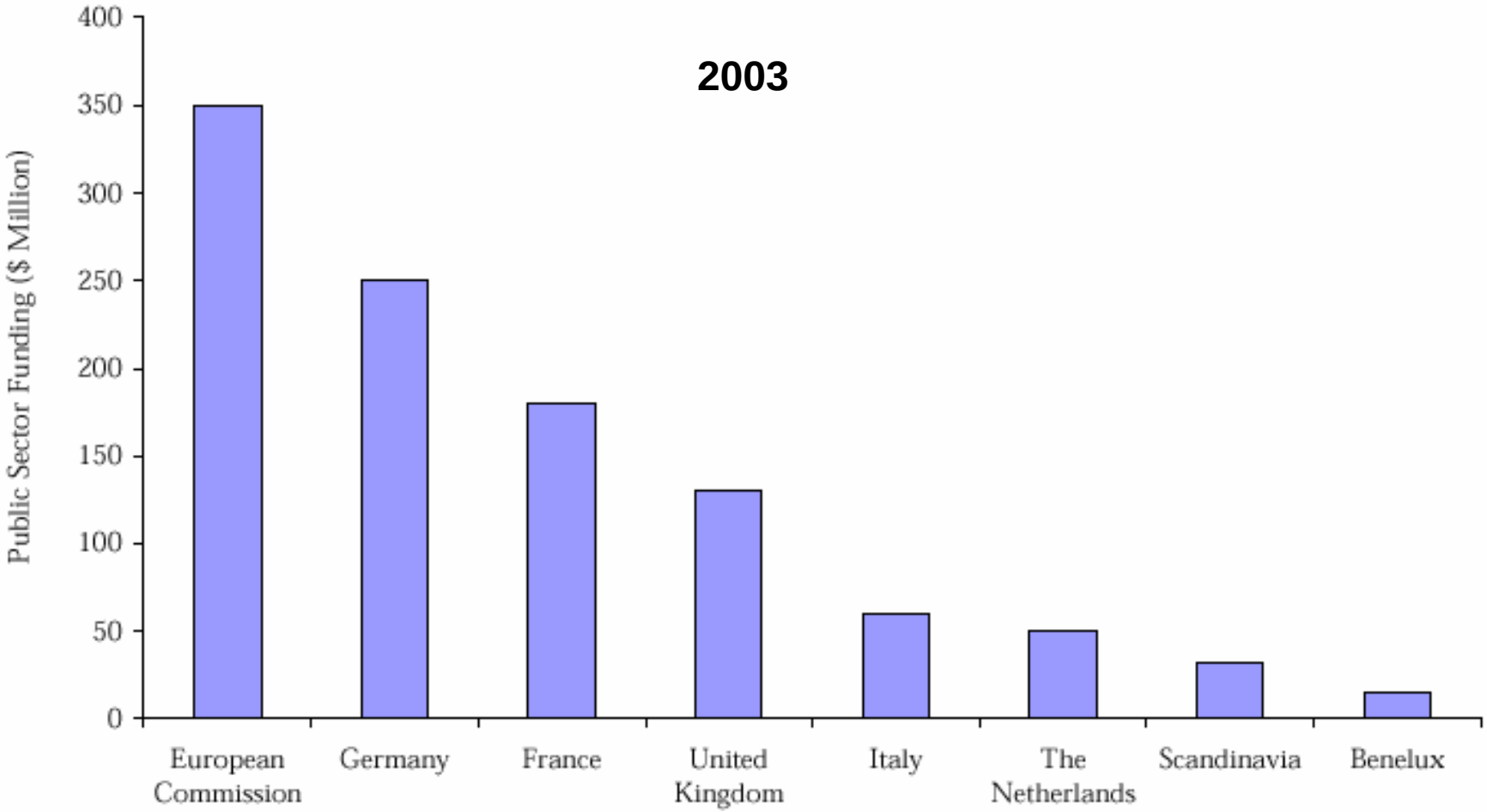
- Nanotechnology is now one of the main Science and Technology priority areas for Asia Pacific governments.
- Budgets for nanotechnology R&D have been increased substantially and more strategically allocated.
- Total spending for Asia Pacific countries has exceeded US$1billion for the past 2 years and will continue to increase.
- Japan has been investing in nanoscience since the 1980s and is the heaviest single country nanotechnology R&D spender worldwide, and along with China, South Korea and Taiwan has increased it budget substantially since 2001.

Nanotechnology in Asia / Pacific

- Japan
  - Allocated $810 million to nanotechnology in 2003 (more than the US).
  - Nanotechnology Research Institute (NRI) is the main collaborative organisation.

- China
  - Allocated $240 million to nanotechnology between 2003-07.
    - Setting up a National Nanotechnology Centre.

Nanotechnology Government Funding in Europe



Market data from Frost & Sullivan

Nanotechnology Funding in Europe

- The most active EU country in nanotechnology is Germany:
  - Federal Government has fostered competence centres and provided around $250 million funding in 2003.
  - $70 million was allocated to nanobiotechnology in 2004 to fund start-up companies and promote research centres over the next 2 years.
- France:
  - Government allocated around $180 million for nanotechnology in 2003.
  - National Nanosciences Programme dedicates around $22 million per annum to nanotechnology with an emphasis on nanomotors and nanobiosensors.
  - National Nanotechnologies Facilities Network has a budget of $190 million over 3 years (2003-05) for the establishment of 5 centres of excellence in nanotechnology.

Nanotechnology Funding in Europe

- UK
  - Government invested around $130 million in nanotechnology in 2003.
    - University Innovation Centres in Nanotechnology at Newcastle and Durham.
    - $16 million Imperial College London Centre for Nanotechnology.
    - $33 million Interdisciplinary Research Collaborations (IRCs):
      - Bio-aspects of nanotechnology (Univ. Oxford).
      - Physical properties of nanostructures and devices (Univ. Cambridge).
  - In 2003 the UK government announced it would be injecting $164 million over the next 6 years towards nanotechnology R&D and commercialisation.
  - Dept Trade and Industry (DTI) announced $140 million between 2003-08 to establish a UK Micro and Nanotechnology Network (MNT)
    - $27 million of this has supported industrial nanobiotechnology projects.

Nanotechnology Funding in Europe

- Scandinavia:
  - Norway
    - Two Government initiatives with nanotechnology components.
  - Sweden
    - 4 publicly supported research institutes investigating nanotechnology.
    - PronanoAB promotes nanotechnology research.
  - Denmark
    - $10 million allocated in 2003 to set up 3 nanotechnology centres (Lyngby, Copenhagen and Aarhus/Alborg).
  - Finland
    - Allocated $93 million in nanotechnology ($33 million for research) between 2005-09.
- Benelux
    - Integrated Nanotechnology Network has been set up in the Walloon region.