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Roadmap Report on Dendrimers

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The present document is a roadmap report prepared by Willems & van den Wildenberg (W&W) in the framework of the NanoRoadMap (NRM) project, co-funded by the 6th Framework Programme (FP6) of the European Commission.

This roadmap report is mainly based on the input received from experts participating in a Delphi-like panel. In addition, W&W has added where relevant its views and opinions, in each case identifying clearly the status of such statement. The views expressed do not necessarily reflect those of the European Commission.

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1 Introduction

1.1 Background

The NanoRoadMap (NRM) project, co-funded by the European Commission (EC), is aimed at roadmapping nanotechnology related applications in three different areas:

- Materials
- Health & Medical Systems
- Energy

Within the project, an international consortium consisting of eight partners covering seven European countries and Israel has joined forces to cover the timeframe for technological development in this field up to 2015. The results of the NRM project are to be used by any European entity interested in planning an R&D strategy taking into account nanotechnology. An important potential user is of course the EC itself in the preparation of the 7th Framework Programme (FP7) for research and technology development.

For additional information on the NRM project, please refer to www.nanoroadmap.it

1.2 Goals

The primary objective of NRM is to provide coherent scenarios and technology roadmaps that could help the European players to optimise the positive impact of nanotechnology on society, giving the necessary knowledge on its future development and when technologies and applications will come into full fruition.

The key users of the reports are mainly European industry including SMEs, research organisations, and public bodies in general and the EC in particular.

This report is one of the three final deliverables of the NRM project (together with the reports on the fields of Health & Medical Systems and Energy) and it is aimed at providing a thorough overview of specific topics selected for roadmapping within the field.

1.3 Methodology

1.3.1 Collection and synthesis of relevant existing information

A report was published in October 2004, as the most important deliverable of the first stage of the project. It was based on the collection and synthesis of existing public sources in 31 countries and was published as key input for the celebration of the First NRM International Conference held in Rome the 4th – 5th of November 2004. The full report can be downloaded for free on the project web site.

The report focused on reviewing the different types of nanomaterials, describing the topic, its most remarkable properties, current and future markets & applications, and leading countries & highlighted R&D activities in the field. A general review of non-

technological aspects (social, legal, ethical and health and safety aspects, but also economical aspects and infrastructures requirements) was also performed.

The 12 topics identified, even if not being completely homogenous in terms of scope or materials classification, were intended to adequately cover the field of nanomaterials. The following list was agreed upon the different partners of the NRM project (similar classifications can be found in the existing bibliography):

- Nanostructured materials
- Nanoparticles / nanocomposites
- Nanocapsules
- Nanoporous materials
- Nanofibres
- Fullerenes
- Nanowires
- Single-Walled & Multi-Walled (Carbon) Nanotubes
- Dendrimers
- Molecular Electronics
- Quantum Dots
- Thin Films

1.3.2 Selection of topics

Another major goal of that report was to set the basis for discussion and selection for roadmapping of 4 out of the 12 topics identified above. A preliminary selection of topics was presented during the First International Conference in November 2004.

After a thorough discussion, which involved international experts in the field of nanotechnology, four topics were selected (and validated in dialogue with the European Commission). The topics chosen are:

- Nanoporous materials
- Nanoparticles / nanocomposites
- Dendrimers
- Thin Films & coatings

1.3.3 Roadmaps elaboration

A Delphi-like approach (hereafter referred to as Delphi panel) has been used for the preparation and execution of the roadmaps. The methodology followed consisted of 2 cycles, and it was the same for the four topics. The Delphi exercise consisted in:

1. Selecting top-international experts in the field (see the annexes for more information)
2. Preparing a dedicated on-line questionnaire for each topic to be roadmapped
3. Circulating the questionnaire and gathering experts' responses (1st cycle)

4. Preparing a first draft roadmap document based on the input gathered from the experts and personal interviews with some experts
5. Circulating the draft roadmap document, asking for feedback (2nd cycle)
6. Elaborating the final version of the roadmap

One roadmap has been prepared for each of the four aforementioned topics. These roadmaps are/ have been presented in 8 National Conferences and one International Conference during the 4th quarter of 2005.

1.4 Structure of this report

This roadmap begins with the definition of *dendrimers* (section 2.1) and the identification and description of their most remarkable properties (2.2). Wherever possible, concrete applications have been linked to potential offered by new or improved dendrimer properties – with respect to other (nano)material categories.

Section 2.3 focuses on the dendrimers' pipeline, including synthesis (2.3.1), functionalisation (2.3.2) and application (2.3.3) steps. For each of these steps, we have detailed most relevant technologies and main barriers pointed out by the experts. Whenever possible, we have also identified ways to overcome these (breakthroughs). In the applications section, we have provided a list of the most common dendrimer applications being researched worldwide. Detailed graphics (based on the input from the experts) provide an overview of the (estimated) state of development of these applications in 2005, 2010 and 2015. Additionally, we have included a graph representing the risk involved against the expected market growth of each application during the next decade.

The next section (2.4) provides an estimated evolution of price and worldwide volume production of certain types of dendrimers. Section 2.5 briefly reviews non-technological aspects of dendrimers. We have not focused in this chapter too much, since other initiatives / projects already cover them.

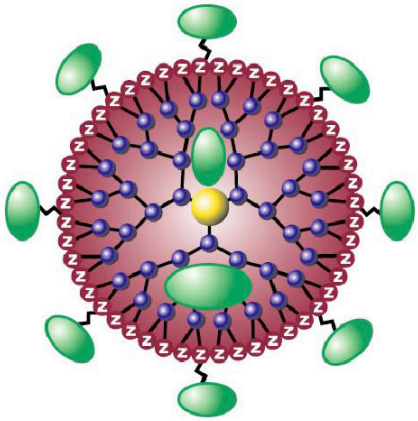
The last section (2.6) is devoted to conclusions and recommendations. It includes the review of the most relevant applications (2.6.1), the evaluation of EU positioning in the field (2.6.2) and final conclusions and recommendations (2.6.3). Annexes at the end of the document include the list of participants in the Delphi panel and a few statistics worth mentioning.

In this document, certain pieces of text have been highlighted to capture the reader's attention. Text highlighted reflects that, according to W&W's opinion, there is a topic there suitable for future FP7 research.

2 'Dendrimers' Roadmap

2.1 Definition of dendrimers

A dendrimer is generally described as a macromolecule, which is characterized by its highly branched 3D structure that provides a high degree of surface functionality and versatility. Its structure is always built around a central multi-functional *core molecule*, with *branches* and *end-groups*.



Courtesy of Dendritic NanoTechnologies, Inc

Dendrimers can be made out of virtually anything that can branch (metal atoms, organometallic groups, or purely organic materials) and they can have a variety of functionalities depending what they are built of and how. Dendrimers are synthesised in a stepwise manner through a hierarchical self-assembly process, in which additional iterations lead to higher-generation dendrimers. The molecule becomes more sphere-like, when the number of generations increases.

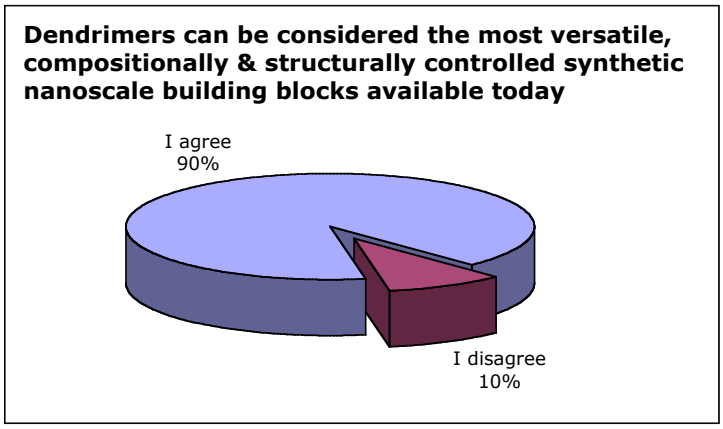
Dendritic polymers are recognized as the fourth major class of macromolecular architecture (together with linear, cross-linked and branched architectures), consisting of four sub-categories: random hyperbranched, dendigrafts, dendrons and dendrimers. This roadmap deals primarily with the field of dendrimers.

The principal difference between a dendrimer and other hyperbranched polymers is that each of the monomer units in the dendrimer has at least one functional unit that allows further branching. Hyperbranched structures can be thought of as somewhere between dendrimers and linear polymers. Some hyperbranched structures have a similar structure to that of dendrimers (apart from the centre of their architecture), but with parameters not as easy to control as in real dendrimers. Synthesis of this type of structures requires less effort and on the other hand can lead to derivatives with certain useful *defects*. The lower cost of hyperbranched polymers has led to their use as composite additives, in preference to dendrimers, in some cost-sensitive applications (e.g. in the auto industry). In other cases, however, the *monodispersity* (consistency of shape and form between molecules) and higher *polyvalency* (more reaction sites) of dendrimers offer advantages justifying the extra cost.

2.2 Most remarkable properties of dendrimers

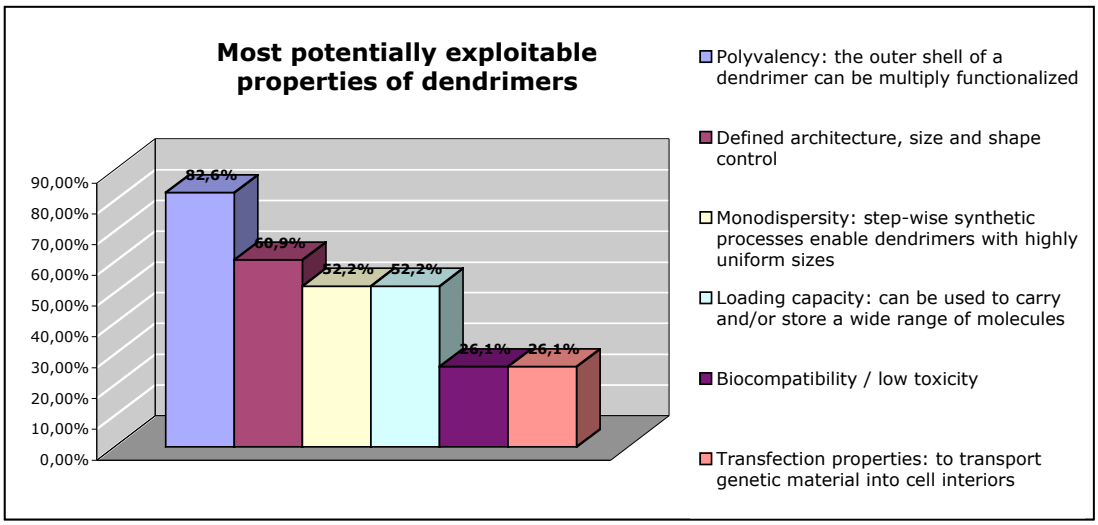
Dendrimers can be considered, according to most (90%) experts consulted, the most versatile, compositionally and structurally controlled synthetic nanoscale building blocks available today. In itself perhaps not too surprising given the fact that all experts are working on dendrimers, the argument used is the following. When comparing dendrimers with other nanoscale synthetic structures (e.g. traditional polymers, buckyballs or carbon nanotubes), these are either highly non-defined or have limited structural diversity. It should be said, though, that a lot of the synthetic

steps applicable to dendrimers can be applied to functionalised buckyballs, but dendrimers offer the potential for variation from the very first synthetic generation.



As a result of their architecture and construction, different dendrimers can possess inherently valuable physical, chemical and biological properties applicable to a whole range of applications that cannot be accessed using normal linear macromolecules. Dendrimers allow selective functionalisation and tailoring of size dependent properties in a very precise and uniform manner.

According to the experts in the Delphi panel, the most remarkable properties of dendrimers are (in order of expert-rated importance):



Polyvalency

The outer shell of a dendrimer admits functionalisation fairly easily, allowing multiple functionalities to be added. Polyvalency is useful as it provides for versatile functionalization; it is also extremely important to produce multiple interactions with biological receptor sites, for example, in the design of antiviral therapeutic agents. Using dendrimers as a scaffold to present multiple copies of a surface group or groups, new biological activities are uncovered with unique pharmacokinetics. Different ligands can be coupled to dendrimers to use them as transfection reagent, e.g., ligands recognising only the surface of a certain cell type combined with ligands that facilitate the escape from the *endosome*.

Functionalisation of the periphery can also result in copolymers with interesting properties, such as viscosity, stability, etc., and dendrimer fillers are already fairly widely used in composites and other materials to modify such properties. Dendrimer properties can be easily tuned by modifying the end groups (e.g. changing the end groups on a same skeleton induces solubility in organic solvents, in CFC or in water).

Metal functionalization of the periphery has applications, for example, in catalysis. Other applications include sensing, nanoscale templates, ionic conductivity and photonic or electronic applications (e.g., enhancement of the electronic transfer: amplification effect, or, for optical applications, light funnelling). Easy functionalisation is also key to enabling compatibility with other materials (e.g., within an opto-electronic device), which is perceived by the experts as a key differentiator from competing materials / technologies.

The high number of reaction points can also allow dendrimers to concentrate materials. This has been used to concentrate nucleic acids to allow detection without use of amplification (i.e. with PCR) and also to combine in one structure multiple, closely held MRI contrast agents.

Defined architecture, size and shape control

Dendrimers branch out in a highly predictable fashion to form amplified three-dimensional structures with highly ordered architectures. This property is relevant for applications such as protein modelling or catalysis. Size control is also important in therapeutic applications, as different molecular sizes exhibit different pharmacokinetics. Other dendritic polymers such as *dendronised* polymers or hybrid linear-dendritic structures can have more potential than pure dendrimers for certain medical applications, but a key requirement for biological applications will be the ability to deliver a pure product, hence hybrid dendritic structures for such applications will generally start with dendrimer construction followed by the hybridisation phase.

The shape persistence of dendrimers is very important, as it allows the defined placement of functions not only on the dendrimer surface but also inside the dendritic scaffold. This is of crucial importance for several applications, e.g. in sensing. Here, the shape persistent dendritic scaffold can prevent self-aggregation of peripherally attached *chromophores*, resulting in high fluorescence intensity of the particles. Furthermore, stiff dendritic architectures possess defined pores or voids. This is a prerequisite for defined interactions between the dendrimer and incorporated guest molecules.

In the context of liquid crystal systems, this property allows the design of Liquid Quasi Crystals (QC). Inorganic QCs are interesting because of their particular (e.g. mechanical, optical) properties. According to some experts, dendrimers are the only organic material that has these properties. Furthermore, dendrimers have potential for the design of flexible displays. Soft self-assembly of dendrimers allows the tailoring of electronic properties in complex systems (multiple functionalities) with a precision approaching that of biological systems. According to the same source, the design of macromolecular devices (machines, motors, etc.) will be quite likely associated with dendrimers, which represent a significant step towards the creation of nanostructured complex systems.

Monodispersity

Step-wise synthetic processes enable the production of dendrimers with highly uniform sizes with defined surface functionality. Monodispersity offers researchers the possibility to work with a *tool* for well-defined scalable sizes. Judiciously performed assembly of components results in dendrimers of desired size and shape, for varying transport and penetration ability. This property is useful for applications such as the synthesis of container molecules, use as templates or in electronic applications.

Monodispersity is, according to some experts, one of the most important differences between dendrimers and polymers. Well-defined structures are particularly important for biological and medical applications.

Loading capacity (molecular container property)

In addition to carrying materials on their surface, the internal cavities of dendritic structures can be used to carry and/or store a wide range of metals, organic, or inorganic molecules by encapsulation and absorption. The appropriate type (and degree) of functionalization results in the desired loading capacity. This property makes dendrimers very suitable as drug delivery vehicles and also appropriate for obtaining electro-optic or magnetic devices. It also allows the use of dendrimers to store, for example, nanoparticles of metal and to prevent precipitation, allowing for the creation of dispersions of what some have called 'nanoreactors'. The possibility of loading dyes could lead to novel ways of labelling and has been used to colour polymers with a dendrimer additive (dendrimers can mix and bond better than the raw dye filler). The possibility of transporting materials makes dendrimers an attractive potential carrier in biosubstrates or an additive for special materials.

Biocompatibility / low toxicity

Some dendrimer systems display very low toxicity levels – with dendrimers carrying anionic groups being less toxic than those carrying cationic groups. Dendrimers commonly show also negligible or very low immunogenic response when injected or used topically. These properties make them highly suitable for drug delivery and biolabeling. In this sense, high biocompatibility is crucial both for preventing toxic reaction and for seeking biodegradability options. Dendrimers can, of course, be made from biomaterials themselves, with DNA being a popular choice.

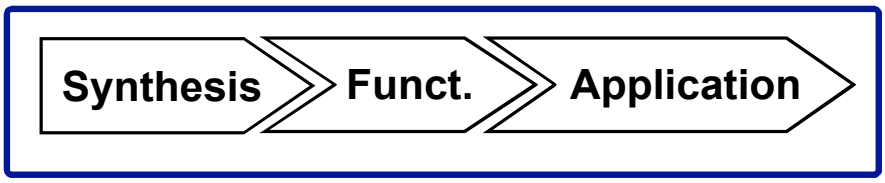
Dendritic polymers have great potential in various kinds of therapies, especially given their ability to be designed for biological specificity, therefore their biocompatibility and lack of toxicity is important. However, not all dendrimers are biocompatible nor show low toxicities. Only some dendrimers have these properties. As said, dendrimers carrying cationic groups can have significant toxicities.

Transfection properties: to transport genetic material into cell interiors

The high diversity of chemical structures possible in dendritic architectures enables the design of selected macromolecules that are able to pass through membranes. Dendrimers have been applied in existing products, for example, to transfect eukaryotic cells in vitro (e.g., SuperFect, PolyFect). Feasibility of these products has already been demonstrated, while benefits have been generated with these dendrimer-based products.

2.3 The dendrimers' pipeline

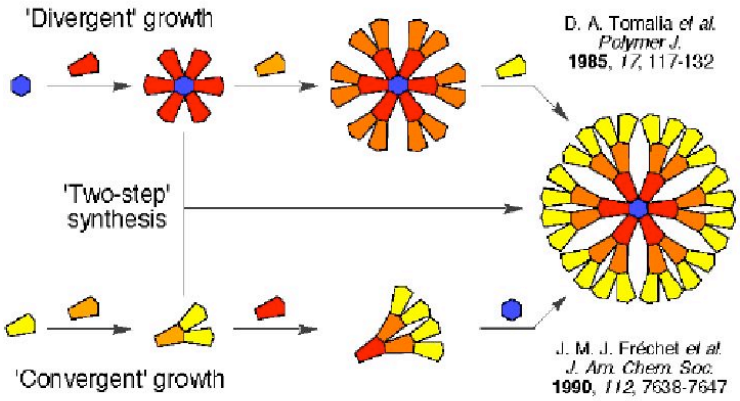
This section reviews the different steps in the dendrimers' pipeline: synthesis, functionalisation and application. Following their synthesis, dendrimers are typically functionalised accordingly to the features the researcher wants them to display and the final application they will fulfil. Finally, dendrimers are incorporated into the final product (application):



However, it should be noted that this is not always a linear approach with sequential independent steps. In many cases each and every different application has one or a few specific production, purification and functionalization processes to obtain the desired properties for either the lowest amount of time and money (e.g. materials applications) or the best functionality and quantity (e.g. biomedical applications). It is therefore not possible to optimise all these steps independently and the best approach is an integral one.

2.3.1 Dendrimer synthesis

Dendrimer synthesis can be achieved through different methods. However, divergent and convergent synthesis are the most common and extended methods. According to the experts in the Delphi panel, the main barriers for the success of dendrimer synthesis methods can be considered the elevated price (though some reasonably-priced dendrimers have been around for some time) and some technical barriers. The main technical challenges for dendrimer synthesis, be that convergent or divergent, are found in establishing process control methods, specifications and final product analytical methods so that the synthesis gives reproducible, high purity and well defined products. It is difficult to anticipate when these barriers could be overcome, as the technical issues mentioned above are faced anew for each type of dendrimer. Thus, it depends very much on when each application of a new dendrimer architecture is pursued. The type of application dictates whether high-volume production and low price are important factors of not. In limited cases, the lack of improved equipment can also be considered a significant barrier.



Courtesy of Andy Shipway

Divergent synthesis

In the divergent approach, the synthesis starts at the core and works its way out to the outer part of the dendrimer. The core, which contains multiple reaction sites, is treated with an excess of the first monomer reacting with all the core's reaction sites. This monomer also has additional reactive groups. An excess of a second monomer is reacted with the half generation (core and monomer), giving rise to the first generation. A continuation of this iterative process leads to higher generations. It is with these higher generations that most types of dendrimers become rather globular and some of their unique properties show.

It needs to be said that there are two main divergent routes that have been reported in different papers (Tomalia–Vögtle and Denkewalter–Newkome). The picture and the text above refer to the Tomalia (PAMAM) structure, which is based on this commercial, readily available material. There is a subtle but important difference between Tomalia and Newkome divergent processes: in the initial Vögtle–Tomalia routes branching occurs at the surface substituent(s), whereas the Denkewalter–Newkome approaches involved a single surface attachment and the monomer possesses the 2- or 3-branching centre, respectively. According to the experts following the latter approach, this could eventually lead to higher yield (no reversibility, higher monodisperse products, greater purity for eventual drug encapsulation) and more thermally stable materials. According to the same sources, this route could have greater commercial possibilities and ease in synthesis.

Cost effective & selective purification can be considered the key technical barrier in most high-generation dendrimers synthetised using the divergent synthesis approach.

In divergent synthesis, the efficiency of each reaction cycle is very important. After each generation, there is a need to eliminate the excess of reagents (due to similar polarity, the purification from precursor molecules and partially reacted products is difficult). High generation dendrimers typically show defects on the surface (defects at early generations lead to highly defect structures). Nevertheless, divergent synthesis strategies remain the preferred methods for commercial production of dendrimers.

Price is always an issue in multi-step syntheses. Some dendrimers can already be prepared with minimal excess of reagents and simple purification techniques. The solution is to limit the size of the molecule (therefore, limiting the number of generations of growth); often this is enough in terms of numbers of reactive end groups. If size is needed, they can be conjugated with (natural or synthetic) macromolecular components.

But, is there really a need for high generations dendrimers? According to some experts, the highest generation having practical applications (except for calibration applications) is the 6th generation (G6) dendrimers (for transfection applications). Furthermore, and still according to the same sources, even though phosphorus dendrimers have been synthesised up to G12, the highest generation of these showing interesting properties (both for materials science and for biology) is G4. From a medical perspective, some experts agree with the previous argument in that it is unlikely that dendrimers of a generation beyond G4 or G5 will be needed. According to the same source, this is unlikely to be a major issue in the context of new pharmaceuticals given existing developments. Certainly, progress to date has

been sufficient for the initial human clinical trials to proceed to the proof of principle stage relatively rapidly.

For high purity dendrimers with a high control of polydispersity key aspects can be considered the purification of individual generations and additionally the yield of functionalisation reactions.

Convergent synthesis

Convergent synthesis starts at the periphery and finishes at the core. The convergent synthesis involves the creation of dendrons and their assembly around the core. A limited number of reactions is required at each step of the growth process. Convergent synthesis makes it easier to yield the desired dendrimer and have further control over all molecular design parameters.

This approach leads to very fast build-up of larger structures, on the other hand requiring efficient coupling procedures of large molecular fragments, which can be difficult, in some cases. Purification (the amount of reagents needed and the intermediate purification is substantially reduced) and characterisation methods are easier. In addition, since dendrons can be attached to other molecules, this approach gives access to numerous novel architectures.

There are no major technical barriers in convergent synthesis. Only in the case of large dendrons, the coupling to the central core represents substantial difficulties.

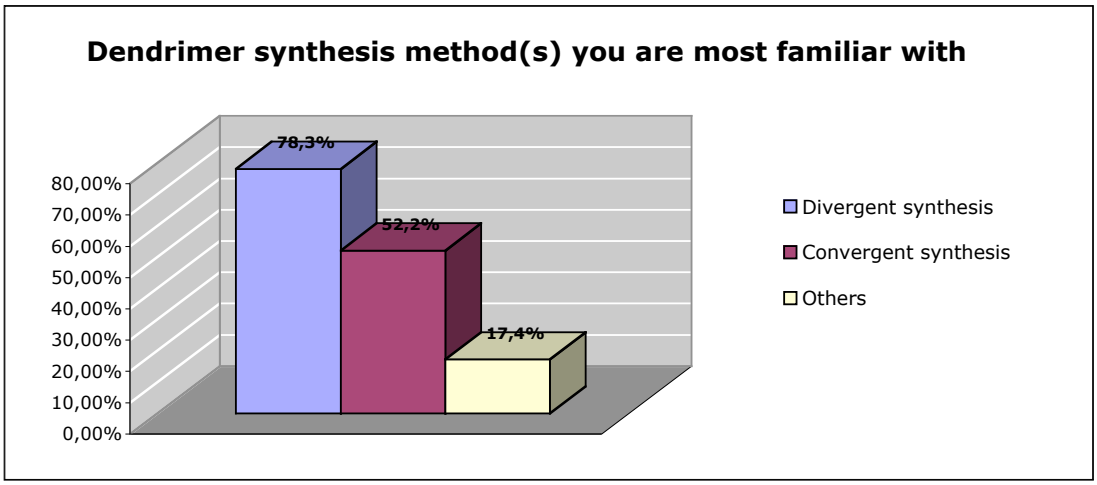
As said, price is always an issue in multi-step syntheses. However, by using convergent methods, low generation dendrimers might be created that can then easily be attached to other macromolecules, if size is desired. For large dendrons, the coupling to a central core is the main issue. This is to be overcome by improved organic synthesis, computer simulation of the behaviour of large systems and their reactivity, which might be of great use in the design of better systems.

In general, it could be said that the convergent approach is appropriate for obtaining small dendrimers while the divergent approach is good for obtaining large dendrimers (which typically show defects). It should be kept in mind, however, that in the convergent paths, dendrons are usually synthesised by divergent paths, so the barriers associated to the latter do usually also apply to the former.

Other synthesis methods

Other synthesis approaches mentioned by the experts in the Delphi panel include combined synthesis (divergent-convergent), dynamic synthesis and double exponential synthesis. According to some experts, the combined synthesis might play a major role in the future reduction of dendrimer costs, since a G4 might be setup from a G2 core and a convergent attachment of a G2 shell (without the need of a G3 intermediate). The conjugation of dendritic fragments to linear macromolecules is also an option to be considered.

According to the experts in the Delphi panel, these are the synthesis methods that they are most familiar with:

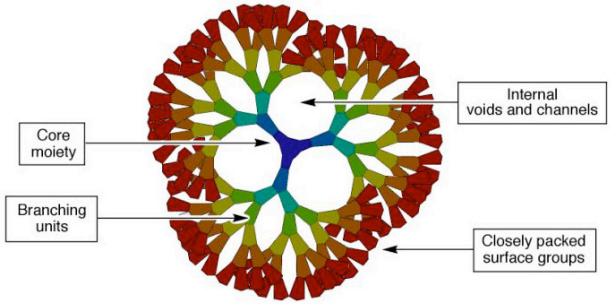


2.3.2 Dendrimer functionalisation

Synthesis > Funct. > Application

Dendrimers can be (relatively easily) functionalised to display features that are useful for the application they will fulfil. Most commonly used functionalisation methods are filling dendrimer cavities, modification of the dendrimer core and modification of the dendrimer surface.

According to the experts, the main barriers associated to dendrimer functionalisation methods can be considered the cost added by the functionalisation, followed by certain technical barriers. Additional information about dendrimer functionalisation methods can be found below.



Courtesy of Andy Shipway

Filling dendrimer cavities

Due to their tree-like structure, dendrimers have internal cavities that can be used to trap small molecules. Customising interior spaces and reactivity allows experts to add extenders or new functionalities to the interior of dendrimers. Dendrimers functionalised this way display customisable encapsulation properties that allow for extended functionalities, depending of the final use that the dendrimers will fulfil.

Modification of the dendrimer core

The overall challenges in the modification of the core or the dendrimer surface can be considered the same: making sure you have control of the synthesis, which can only be assessed with sound analytical methods. A key barrier to success in the modification of the dendrimer core is the limited number of reactive handles at the core of most dendrimers. Once again, this challenge needs to be addressed for each dendrimer application, so no definitive timeline can be given to overcome these barriers.

Although the percentage of final cost added by this functionalisation method depends very much on the dendrimer framework available, the experts in the Delphi panel have estimated it at 20% - 50%.

Modification of the dendrimer surface

Surface properties can be functionalised making use of *capping* reagents on the outermost generation. By doing this, dendrimers may display a novel range of functional properties, including:

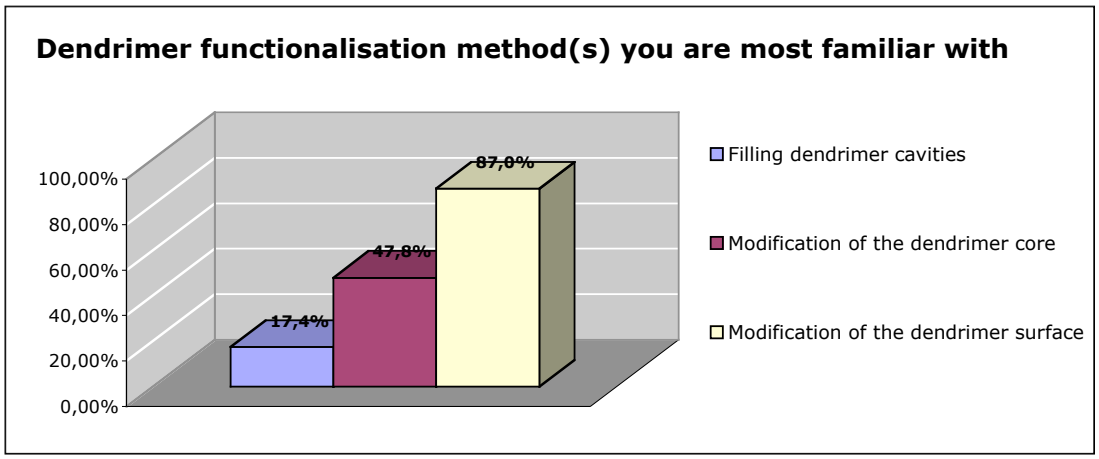
- Polyvalency: the outer shell of a dendrimer can be functionalised to attach reactive groups. Each of these reactive sites has the potential to interact with a target entity, often resulting in polyvalent interactions.
- Flexible charge and solubility properties: through use of appropriate capping groups on the dendrimer exterior, the charge and solubility of dendrimers can be readily manipulated.
- Flexible binding properties: through the use of appropriate capping groups on the dendrimer exterior, dendrimers can be designed to exhibit strong affinity for specific targets.
- Transfection: dendrimers can be designed to move through cell boundaries and transport genetic material into cell interiors.

The functionalisation of dendrimers can be considered relatively easy to perform, when compared to most other nanomaterial categories. In addition, it is possible to verify their degree of functionalisation to a higher degree of accuracy than it is possible with most other nanomaterial categories, in which this is determined based on statistical methods. The functionalisation is usually the key to giving dendrimers the final properties required for the application they will fulfil.

The controlled functionalisation of the surface can be considered a matter of synthetic methodology and equipment. Modification of the dendrimer surface is relatively easily achieved (according to the experts, the easiest of all modification processes) and is straightforward in most cases, depending on the structural features of the dendrimer and the degree of functionalization desired. If full functionalization is required (sometimes not necessary) and if the molecule to be attached at the chain ends is large, steric issues may arise and the problem becomes technical.

The percentage of final cost added by this functionalisation method depends very much on the cost of the capping molecules and the desired degree of functionalisation. As a result, there is a very big variation in the estimations given by the participants in the Delphi panel. Answers given range from few percent to almost hundred percent.

Based on the responses given by the participants in the Delphi panel, these are the functionalisation methods that they are most familiar with:



2.3.3 *Dendrimer applications*

Countless applications involving dendrimers are being researched worldwide. The following is an extensive list of the most common dendrimer applications:

Power/Energy

- Catalytic agent

Healthcare/medical

- Cellular Transport
- Artificial cells
- Diagnostics and analysis
- Targeted delivery (e.g. protein, antibody and anti-inflammatory; nanoparticles, radionucleides, fluorescent markers, etc.)
- MRI contrast agents (e.g. organ, vascular and tumour imaging)
- Transfection reagents, DNA-carriers
- Protein / enzyme mimics or modelling
- Manufacture of artificial bones
- Development of topical microbicide creams; antimicrobial, antiviral (e.g. for use against HIV) and antiparasitic agents
- Biomedical coatings (e.g. for artificial joints)
- Novel polyvalent dendrimer-based drugs
- Artificial antibodies and biomolecular binding agents, e.g. anti-infection and toxin treatment for SARS / bird flu (especially blocking the cytochine storm), biowarfare, antibiotic-resistant drugs, etc.

Engineering

- Molecular weight and size standards
- Chemical / biological sensors & detectors
- Carbon fibre coatings and ultra thin films
- Polymer and plastics additives (e.g. for lowering viscosity, increasing stiffness, incorporating dyes, compatibilisers, etc.)
- Creation of foams (i.e. synthetic zeolites or insulating material)
- Building blocks for nanostructured materials

Consumer goods

- Ink / laser-printing toners
- Dyes and paints
- Industrial adhesives
- Manufacture of nanoscale batteries and lubricants

Environmental

- Decontamination agents (trapping metal ions)
- Ultrafiltration

Electronics / optoelectronics

- Molecular electronics for data storage
- 3-D optical materials
- Light-harvesting systems
- OLEDs (i.e. flat panel displays and other light emission applications)
- Quantum dots
- Liquid crystals
- Printed wire boards
- Low-k materials (i.e. insulation materials)

Others

It is very difficult to generalise about a future in an area that is still developing so much and has applications in such different stages of development. The following paragraphs, however, give an integrated overview of the different stage of development of the applications listed above.

The following three paragraphs each cover one *snapshot* of the overall dendrimer roadmap. One for the current state of the art (2005), one for the state of the art as predicted in five years from now (2010) and one in ten years from now (2015).

The visualisation of innovation funnels in 2010 and especially 2015 might give the erroneous impression that in the future, basic R&D (and in some cases even applied R&D) becomes obsolete. This is of course not the reality. It is important to note that the application status visualized in the funnels represents the advancement of the first pioneer applications; the forerunners of a large field of applications.

In reality, each of the application areas visualized in the funnels is the tip of an iceberg of related applications, and each of them will continue to inspire basic research as well as new possible investigation routes. However, in the Nanoroadmap Delphi exercise, the experts were not asked to identify such new basic and applied R&D areas; they were asked to position the spearhead applications in a relative sense, comparing which ones were expected to reach the market first.

The following distinctions have been made in the next figures:

Basic Research & Development Phase (Basic R&D)

Applications in this phase have received the interest of at least one or more researchers in the world. Some applications might still be in early development, while others are tough to develop and need a lot of basic research to be fully understood. The object of basic R&D is to validate the original hypothesis. Many applications are currently in this phase as researchers are still struggling to understand basic properties of dendrimers.

Applied Research & Development Phase (Applied R&D)

After the hypothesis is validated, research typically (but not necessarily) moves from pure research labs to more commercial labs and companies. Applied R&D will eventually result in a proof of concept, a successful demonstration model. While the production issues might not have been solved yet, a successful prototype / model has been validated.

Production Research & Development Phase (First applications)

After first demonstrator models and prototypes, initial, usually prohibitively expensive, small amounts of products may be produced. At the same time, if these prove successful, companies will seek to upscale production processes. Generally at some point, demand increasing sufficiently to offset the investment needed to start bulk production. This phase ends at that point when is clear and possible to start this bulk production.

Mass production and incremental research (Mass production)

The final development phase, in this phase production has reached bulk amounts and research focuses on incrementally improving the products. After this phase even more phases can be discerned (market maturity, end of life cycle, etc.) but these have not been taken into account when creating the following figures.

Overview of current applications (2005)

The figure in the following page is an overview of the current state of development of different dendrimer applications. The text and the figures presented in this section are mostly based on the input given by the participants in the Delphi panel.

Due to their organized structure, ease of modification and strong adsorption behaviour to a variety of substrates, dendrimers can be used in the manufacturing of sensors to detect e.g. hazardous chemical vapours. Some types of dendrimer-based **sensors and detectors** are already commercial.

The exceptionally uniform molecular size of the various generations of PAMAM dendrimers makes them excellent **molecular weight and size standards** for calibration of analytical instruments. The US administration is already using them for this purpose.

Current applications include also **inkjet inks and toners**. At low levels, certain types of dendrimers dramatically improve water resistance and adhesion of inks to a variety of substrates (e.g., paper, glass, metal or plastic). In toners, they impart good admix and flow characteristics, stable properties, and high image quality.

In the field of *in vitro* **diagnostics**, dendrimer-antibody conjugates are used in an immunoassay for rapid and sensitive detection of markers indicative of heart attacks.

Dendrimers and hyperbranched polymers are already used as **fillers in a number of composites** (improving viscosity or cross-linking and stiffness) and in **paints**, with PPI dendrimers offering good enough prices for cost-sensitive applications. High-performance plastics have benefited from dendrimers as compatibilisers and bonding agents and hyperbranched polymers are in use as toughening agents in epoxy resins.

Some health-related applications are already approaching the first stages of commercialisation. These include, for example, the use of dendrimers as **MRI contrast agents** and **transfection reagents** (DNA carriers). PAMAM dendrimer conjugates with paramagnetic ions, for example, are being studied for their use as magnetic resonance imaging (MRI) contrast agents.

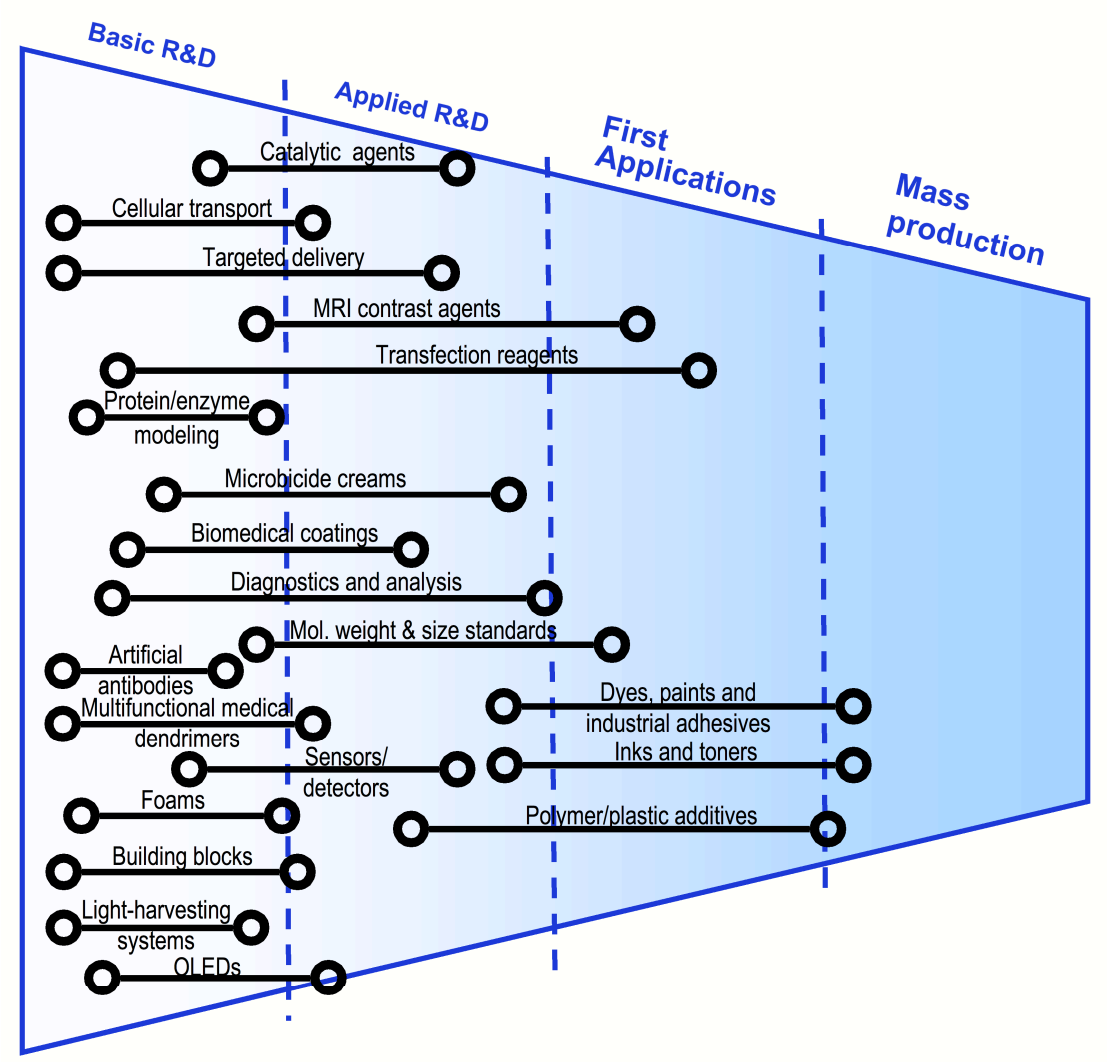
Other uses of dendrimers approaching the first commercialisation stages include, for example, their use as **catalytic agents** (giving homogeneous catalysts that are easily removed, e.g. by centrifugation or ultrafiltration) or into **microbicide creams.**

A lot of applications are, however, in the basic and applied R&D phases. Many of the applications in the medical field still remain in the (pre-)R&D phase. This is the case for certain **targeted drug delivery** applications, **cellular transport** or protein / enzyme **mimicking or modelling**. The use of dendrimers in the creation of **foams**, as **building blocks** for nanostructured materials (a recent development is the growth of carbon nanotubes in low temperatures on dendrimer catalysts) or in **light-harvesting systems** is also in its earlier stages.

Dendrimer research is very much application-oriented. Development timeframes of different applications are difficult to estimate, because barriers are not so much linked to the synthesis or the functionalisation, but to the final application being researched and the cost for a given volume.

Dendrimers are also being used as the basis for **coating technologies**. Dendrimer-based coatings can display many of the same attributes of dendrimers in coating form. They are currently being investigated for applications in nano/microelectronics.

There are certainly many dendrimer-related applications possible. In spite of this, only a small number of them (up to a third, according to some experts) may reach the final market. OLEDs are only one example, facing tremendous competence from other materials such as conjugated polymers.

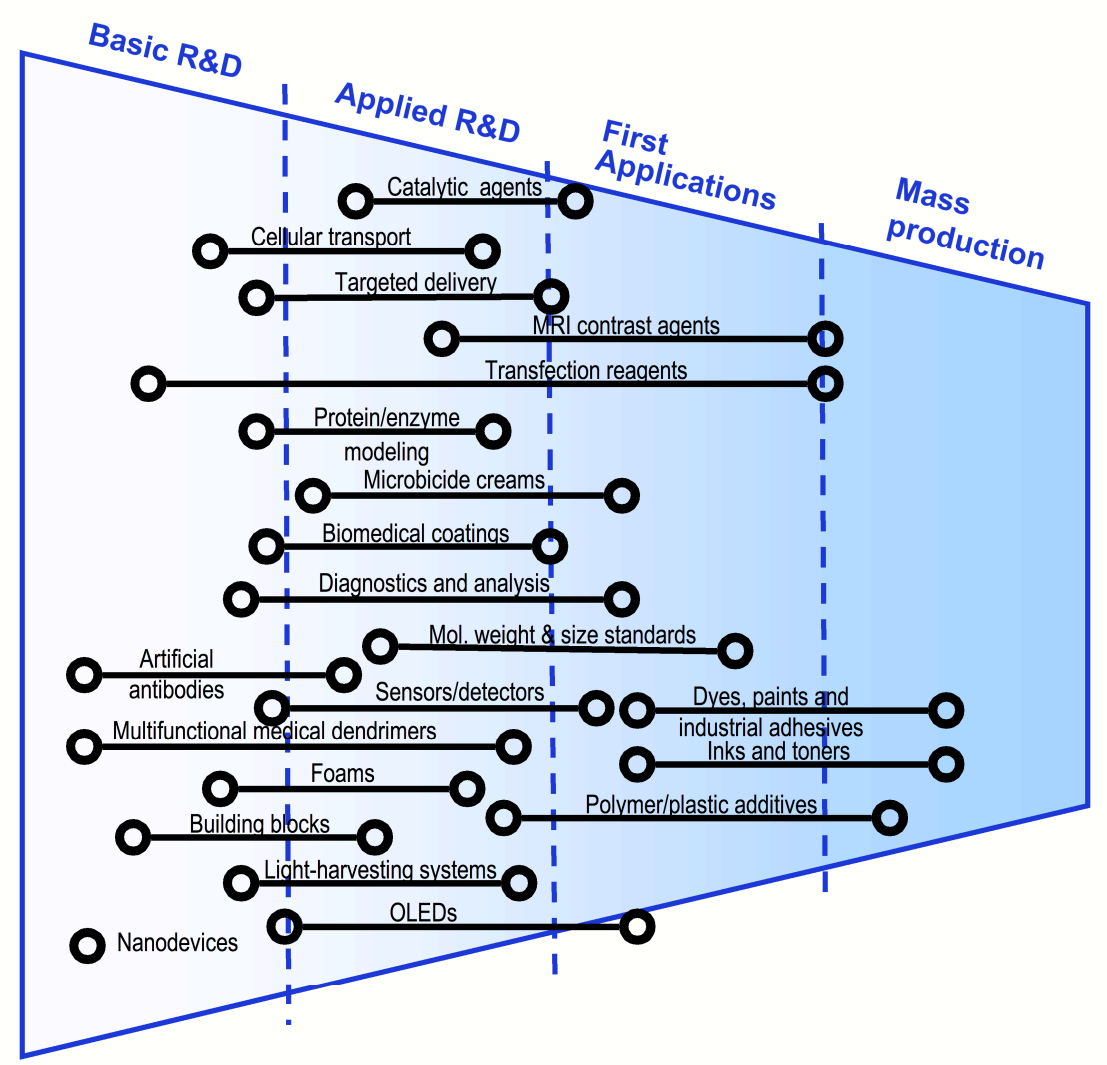


Overview of applications in 2010

The following figure is an overview of the expected state of development of different applications of dendrimers in year 2010. After five years many more applications will have come into fruition. The text and the figures presented in this section are mainly based on the input given by the participants in the Delphi panel.

A good number of the potential applications currently considered would most probably be either in the applied R&D phase or already approaching the first commercial applications.

Future concepts that will enter the funnel of applications in 2010 include nanodevices. Applications that will remain in the basic R&D phases include multi-functional medical dendrimers (e.g. *tectodendrimers* - pioneer is James Baker of Michigan University and NanoBio). Basic to applied now (this is in 2005), it can be expected to approach first applications in 2010, but the basic research will also remain strong for many years.

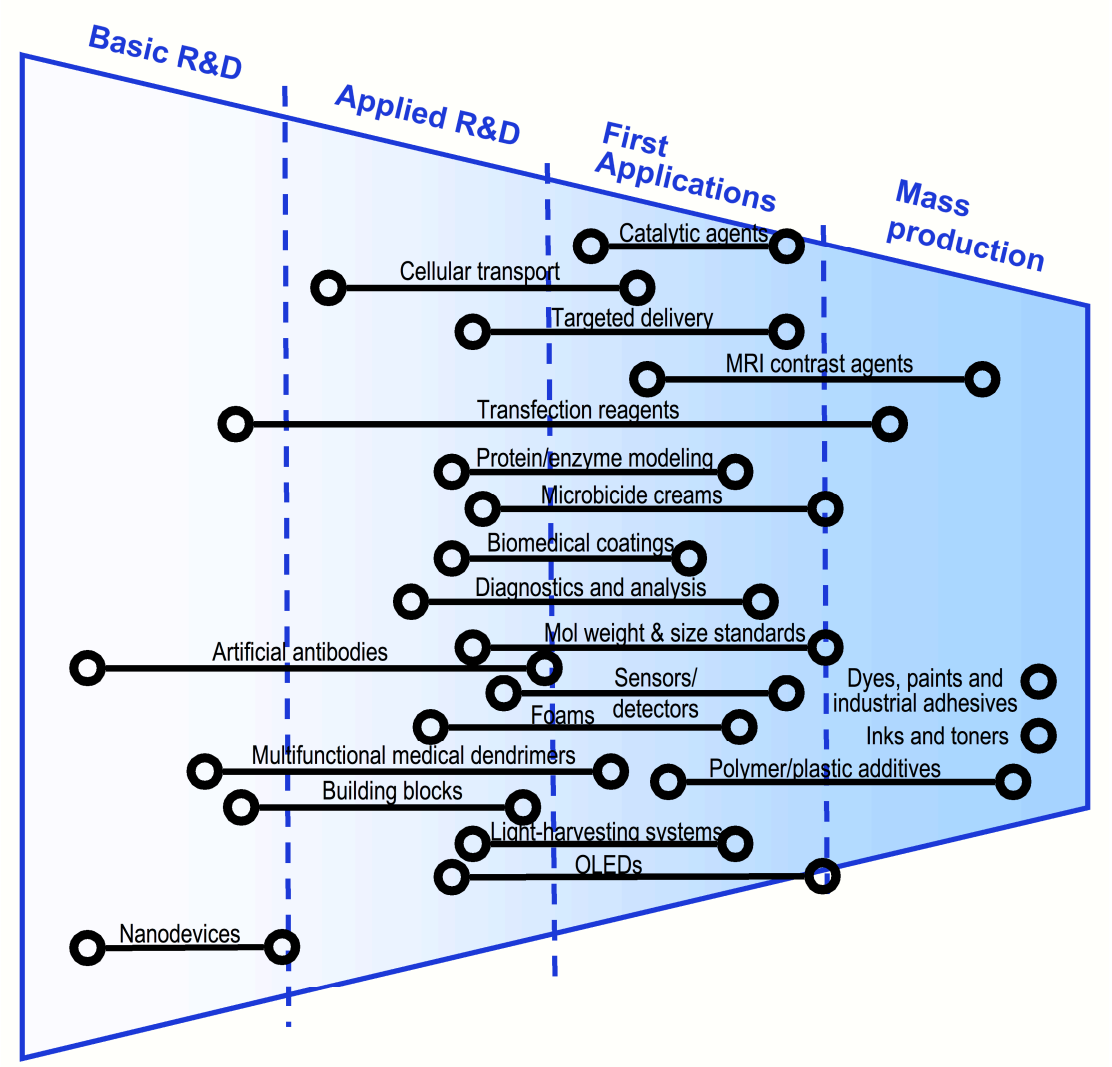


Overview of applications in 2015

The following figure is an overview of the expected state of development of different applications of dendrimers in year 2015. The text and the figures presented in this section are mainly based on the input given by the participants in the Delphi panel.

By 2015 many applications currently in development will be actual markets and currently still wild ideas may be ready to move to the market. Certain specific electronic and medical applications, however, might take even further time to develop. In the case of health-related applications, this might be due to the need to carry out lengthy clinical trials and the need for relevant administration approval.

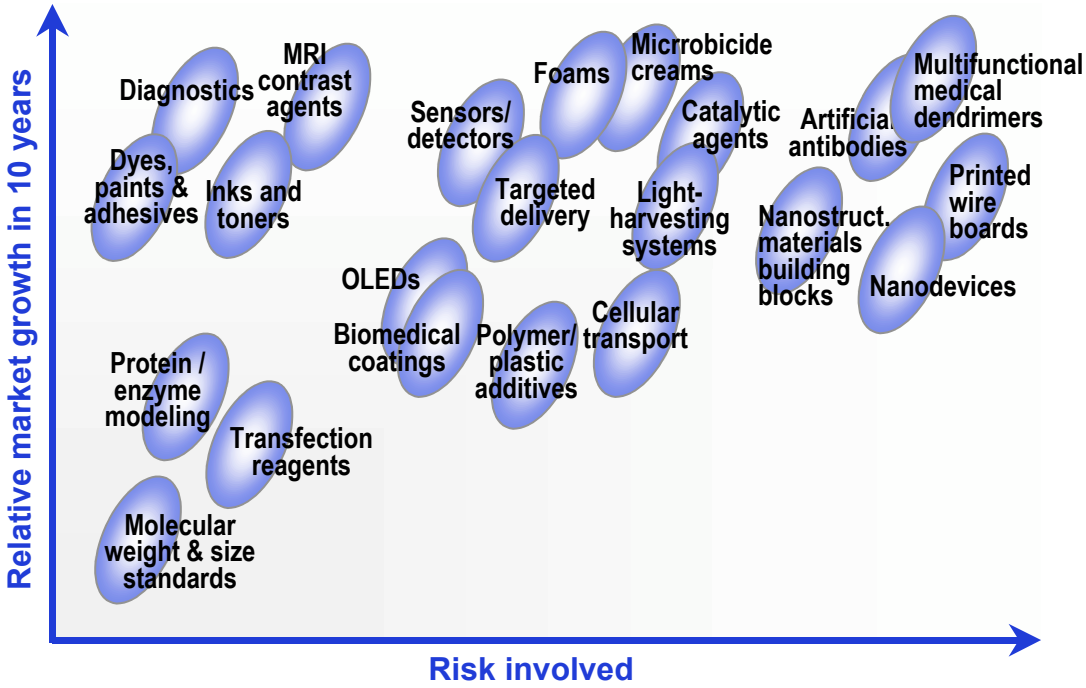
Future research ideas include nanodevices, which may enter the applied research phase by 2015.



Risk involved vs. expected market growth in the next decade

For selected applications the following figure shows an estimation of (technological plus market) risk involved with the development vs. the estimated market growth of that application in the next decade.

The general purpose of the figure is to compare the relative position of different applications. For some applications, the current market of dendrimer-related products is zero while for others, a significant market exists today. Furthermore, the stage of development of different applications has also an impact on the estimated risk (normally, the more advanced the application is, the less risk). However, some applications might face harder restrictions to arrive to the market (e.g. FDA approval for medical applications).



The figure below is based on the input gathered from the experts that have participated in the Delphi panel. Applications on the lower left of this figure have lower risk but also less potential reward since the related market is not expected to grow so much during the next decade. Applications on the lower right (high risk, low market growth) will need substantial support to be developed. More towards the upper left (low risk, high market growth) we would find the most interesting applications. In the upper right we can find applications that combine a high risk with markets that will growth exponentially, if the application develops successfully.

It can be appreciated that there are no applications clearly positioned in the lower right end (clearly unattractive applications). In the upper left end (highly attractive applications) we find medical applications (e.g. MRI contrast agents and diagnostics) and consumer applications (e.g. dyes, paints, adhesives, inks and toners). A common trend observed in the previous figure is that applications with higher expected market growth in the next decade do normally also have higher risks associated.

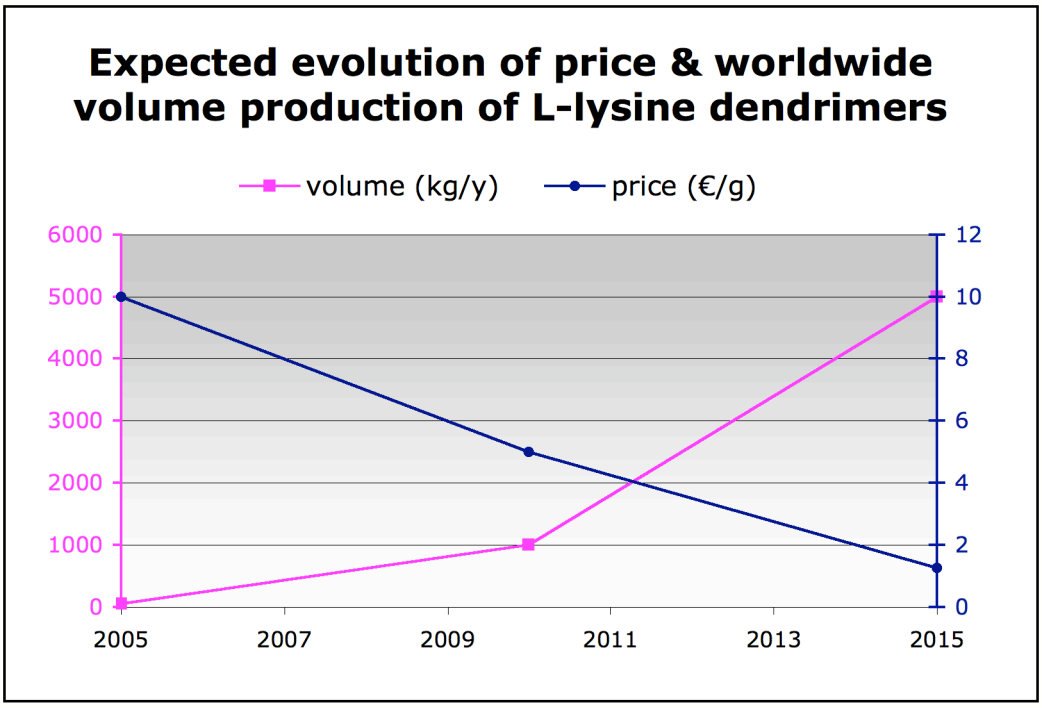
2.4 Estimated evolution of price & worldwide volume production

Although again it is very difficult to accurately foresee a future in a technology area that is still so much developing as dendrimer technology is, estimations on price and worldwide volume production of some types of dendrimers can be quite useful. The following figures have been elaborated based on the indications given by individual participants in the Delphi panel, who have made a laudable effort to provide explicit data for this chapter.

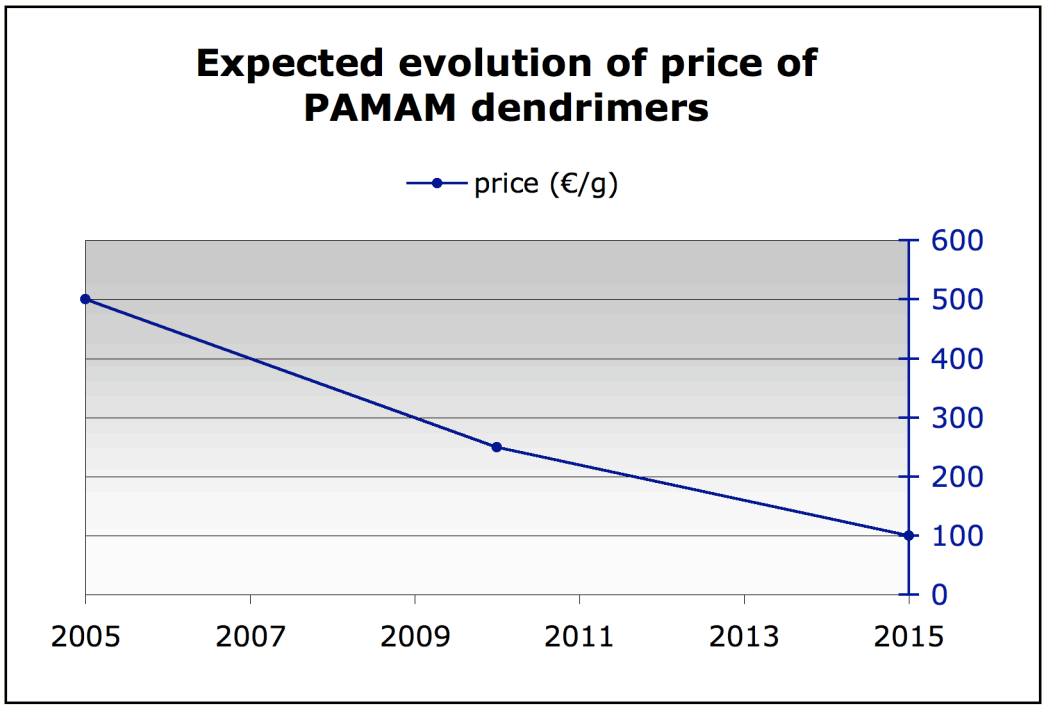
While academic researchers typically do not handle this type of information (estimations), companies are not eager to show everything they can do (or cannot do), mainly for competitive reasons. Furthermore, technological advancements may result in small jumps in production capability that not even the companies themselves have foreseen yet. On the other hand technological hurdles could make the demand for dendrimers evolve more slowly than expected, also leading to less reason to expand production capacities.

Additionally, in almost all the areas in which dendrimers show promise there are competing technologies that could stop dendrimer-based solutions ever being widely commercialised. According to the experts, the areas where dendrimers will most likely achieve sustained commercial success will be those where the application strongly depends on the unique characteristics of dendrimers, such as polivalency.

The following figures are to be used only as an indication of trends in price and volume production curves of these types of dendrimers. For the same dendrimer family, variations exist in price (depending on the generation, quality, etc.). For this reason, data should be only considered as an average indication.



L-lysine dendrimers have use in targeted drug delivery applications. They are also used in the development of topical microbicide creams, due to their superior manufacturability, stability and biological compatibility when compared to other types of dendrimers. The binding of viruses and bacteria to their human host or environment is a polyvalent binding event. This type of dendrimer is an ideal platform from which to develop a polyvalent antiviral or antibacterial to interfere with these processes.



PAMAM dendrimers have countless applications. They have use as catalytic agents and as templates for *nanoreactors* in foams. They are also being used in targeted drug delivery, where the dendrimer acts as precise synthetic nano-containers and nano-scaffolding with non-immunogenic properties, if appropriately designed. They also provide for high loading capacities.

PAMAM dendrimers also have applications as MRI contrast agents. Here, the added value of dendrimers is that they offer increased resolution and better contrast for a lower concentration. PAMAM-based dendrimers with certain functionalisation can bind to / store high amounts of contrast-providing groups.

PAMAM dendrimers also have use as transfection reagents, where nanosized complexes are needed to be taken up by a cell. Partially degraded PAMAM dendrimers are very suitable for this application. According to some sources, the volume of PAMAM dendrimers required for this application can be estimated to be in the lower kg range. This type of dendrimer also has use in diagnostics or as protein / enzyme mimics and in modelling.

2.5 Non technological aspects

This chapter is devoted to Non-technological aspects of dendrimers, including issues related to Health, Safety and Environment (HSE), infrastructure/equipment requirements, instrumentation costs, etc.

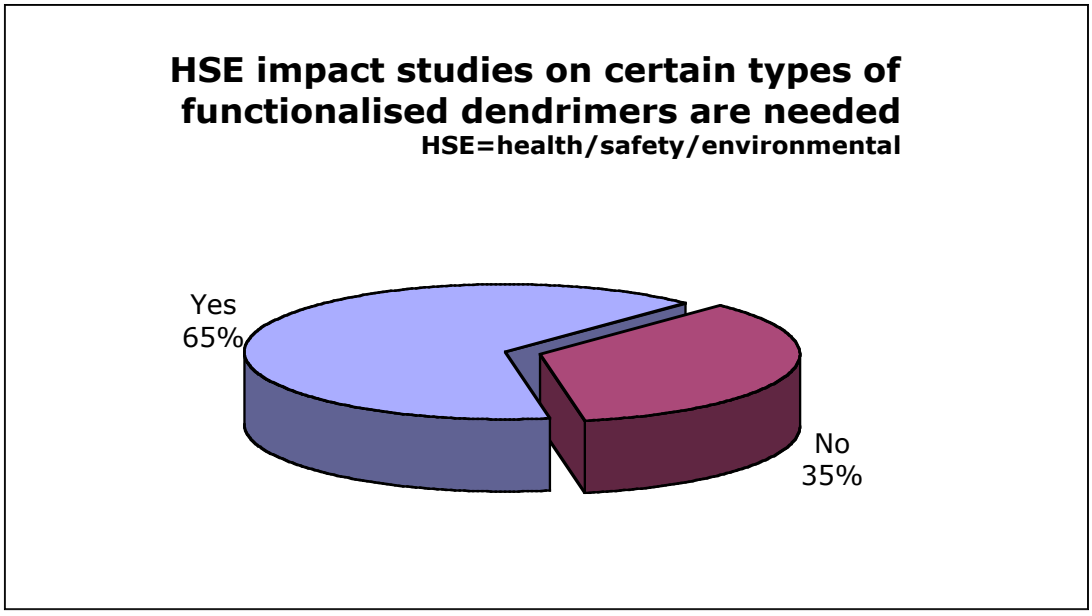
Health, Safety and Environmental (HSE) aspects

A white paper recently published by Cientifica, called *Nanotechnologies: Risks & Rewards* stated *"Many academic establishments and companies have inadequate procedures for monitoring exposure to nanomaterials, leaving them liable for future claims. As a result, some companies working with nanomaterials have seen dramatic increases in their insurance premiums".*

According to the authors, concerns and uncertainties raised, related to health and safety aspects, result in a slower adoption of nanomaterials by the industry. Thus, *"Companies need to understand and clarify the current trends in both toxicology and regulation in order to ensure that they can reap the rewards of nanotechnologies while avoiding the risks, and this needs to be done immediately".*

When enquired about whether HSE impact studies of certain types of functionalised dendrimers are required, 65% of the experts participating in the Delphi panel agree that these types of studies should be performed.

A key consideration here is, according to the experts, who is working with the nanomaterial and how novel this is. Dendrimers are often likely to be developed by companies with good experience of bringing novel chemicals (and dendrimers are exactly that) to market and their synthesis lends itself to established methods of risk evaluation and should be covered by existing safety legislation for chemicals. Other nanomaterials that might present dangers, such as nanoparticles, nanotubes, buckyballs etc. often involve realms and groups with much less of a history. Dendrimers are thus less likely to present surprises in the HSE realm.

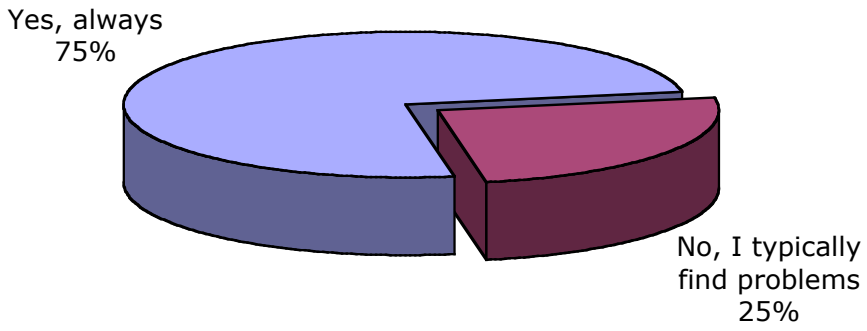


Infrastructure requirements

When asked about infrastructure needs required to perform the nanotechnology day-to-day work, most participants (75%) in the Delphi panel agree that they have adequate access to facilities (either internal or through existing collaborations). Only 25% finds problems.

I have adequate access to infrastructure/equipment required to perform my typical nanotechnology-related activities *

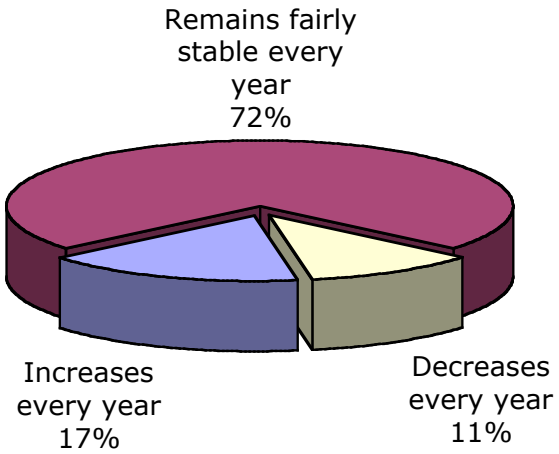
*** Including both own & external facilities (through existing collaborations)**



Instrumentation costs

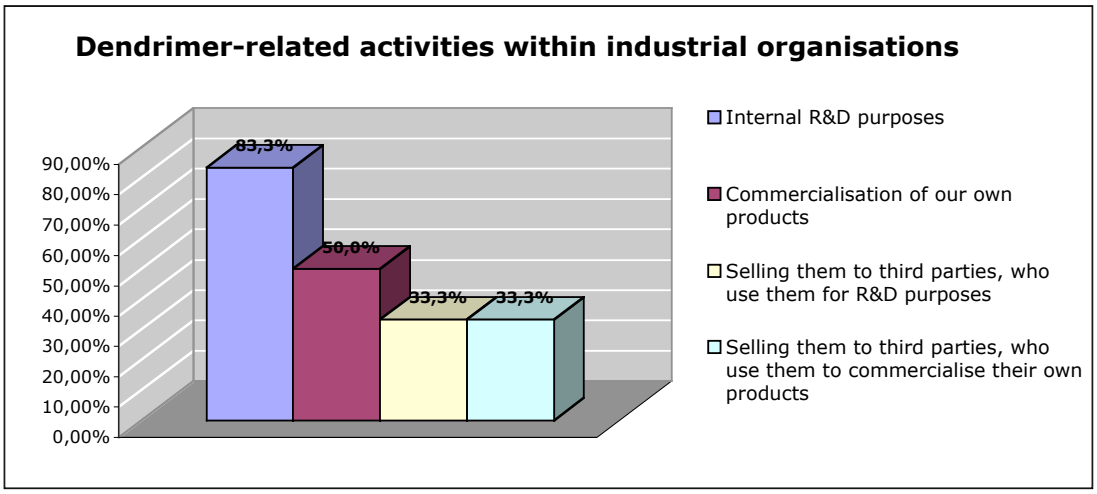
When enquired about price trends of dendrimer-related equipment, 72% of the experts in the Delphi panel indicate that they remain fairly stable from year to year. The other answers are divided between the experts that think that the price increases annually (17%) and those that think it is the opposite way (11%).

Instrumentation costs for the manufacturing, characterisation and manipulation of dendrimers...



Dendrimer-related activities within industrial organisations

In the last years, dendrimers have generated a very high interest throughout the scientific (and increasingly also the industrial) community. The following figure (responses gathered from participants in the Delphi panel) shows the current activities of industrial organisations in the field of dendrimers. It can be observed that companies combine internal research tasks with the commercialisation of its own products and / or the selling of dendrimers to third parties.



2.6 Conclusions

2.6.1 Most relevant applications

The potential applications of dendrimers are almost endless, as already discussed earlier in this document. Materials applications (inks, paints, composites, etc.) are the most commercially advanced but in many cases there are competing technologies. The field of medical applications is at an earlier stage but represents the greatest potential (and with less competing technologies), which is probably not surprising given that dendrimers essentially represent engineering at biological size scales. Applications such as transfection reagents, MRI contrast agents, or microbicide / antiviral / antiparasitic treatments are in full development, with several companies and research groups pursuing them worldwide. In addition, elevated costs associated can be considered a less limiting factor in medical-related applications than in some others fields. This has led to an explosion of dendrimer-related patents in this field over the last several years (much more in the US than in Europe, however).

Investigations of dendrimers as carriers for imaging contrast agents (an early medical application of dendrimers) have demonstrated excellent potential. The use of dendrimers in this application allows for enhanced organ, vascular or tumour imaging and diagnostics. For example, the superior ability to visualize vascular permeability and renal function allows early diagnosis of acute renal failure. A key advantage of dendrimers in this application is the ability to bind to multiple contrast agents and bind them tightly, which improves contrast. Shielding toxic metals is also possible. A competing nanotechnology for MRI uses fullerenes.

Dendrimers have also been used as transfection reagents. PAMAM dendrimers chemically synthesised with positively charged amino surface groups, have been used to deliver nucleic acids. Currently, cationic lipids are the most popular reagent for siRNA transfection, providing a positively charged vehicle to carry the negatively charged nucleic acids into cells. Compared to cationic lipids, these polymer-based reagents display greater transfection efficiency and less toxicity in many cell types. Dendrimer-based reagents are being researched in order to create a more efficient and versatile delivery reagent with low toxicity levels.

Other life sciences applications are also receiving a lot of attention. Targeted drug delivery is one of the most attractive potential applications of dendrimers. The high level of control over the dendrimer architecture makes them ideal carriers for the delivery of active pharmaceutical ingredients. Drugs that have been encapsulated into or attached onto dendrimers include cisplatin, doxorubicin, adriamycin, methotrexate, 5-fluorouracil, ibuprofen, and nifedipine. If successfully developed, the potential reward associated to this application will be huge. Dendrimers may take the place of polymeric agents, but with advantages such as the large number of identical surface groups, excellent encapsulation properties and highly controllable chemistry. On top of this, factors such as the high availability of research funding and the hard commercial push by dedicated companies such as Dendritech also contribute to the development of this application.

Multi-functional dendrimers and dendrimer complexes offer particularly unique potential. A basic targeted delivery example would be a product that combines a molecule targeting a cell surface receptor and payload of some sort (drug, contrast

agent, genetic fragment etc.). These can be combined on one dendrimer but an easier synthesis path is to functionalise dendrimers independently for the two desired functions and then join them into a complex. Multifunctional dendrimer complexes are being pursued that will identify a target cell, deliver a payload, detect whether it has had the desired action and then communicate this to the outside world - four functions in all. NASA is working on trifunctional dendrimers that target white blood cells, detect apoptosis (cell death) and fluoresce. This can be used to detect early signs of radiation damage in astronauts with a simple retinal scanner.

The approach of combining dendrimers with different functions to make a supramolecular agent suggests the possibility of creating a 'toolkit' of the singly-functionalised dendrimers that can be mixed and matched with other existing or new functions as desired.

It should always be remembered that medical applications will require official approval by relevant administrations (e.g. the FDA – Food and Drug Administration in the US) before being commercially implemented. In July 2003 the FDA allowed the first clinical trials of a dendrimer based pharmaceutical: Vivagel™, a topical microbicide for the prevention of HIV infection in women developed by the Australian company Starpharma. Phase I clinical trials of Vivagel™ are currently underway.

Another area receiving a lot of attention is electronics, with sensing applications being a bit more advanced than others. Some very good work is also being performed in light-harvesting and light-emitting macromolecules. IBM has a strong interest (and lots of patents) on the application of dendrimers in micro- and molecular electronics. Attempts are being made to exploit the three-dimensional shape of dendrimers is in generating porosity in low-k (highly-insulating) dielectric materials and dendrimers are being explored in plastic electronics.

There are a number of commercial dendrimer-based products that are just starting to appear. The Swedish company Perstorp sells dendrimer-like materials for a variety of applications, high performance varnish for boats being only one example. DSM, in the Netherlands, has a new type of dendritic-based material that promises to reduce the number of steps in the papermaking process, making it much more efficient and environmentally friendly.

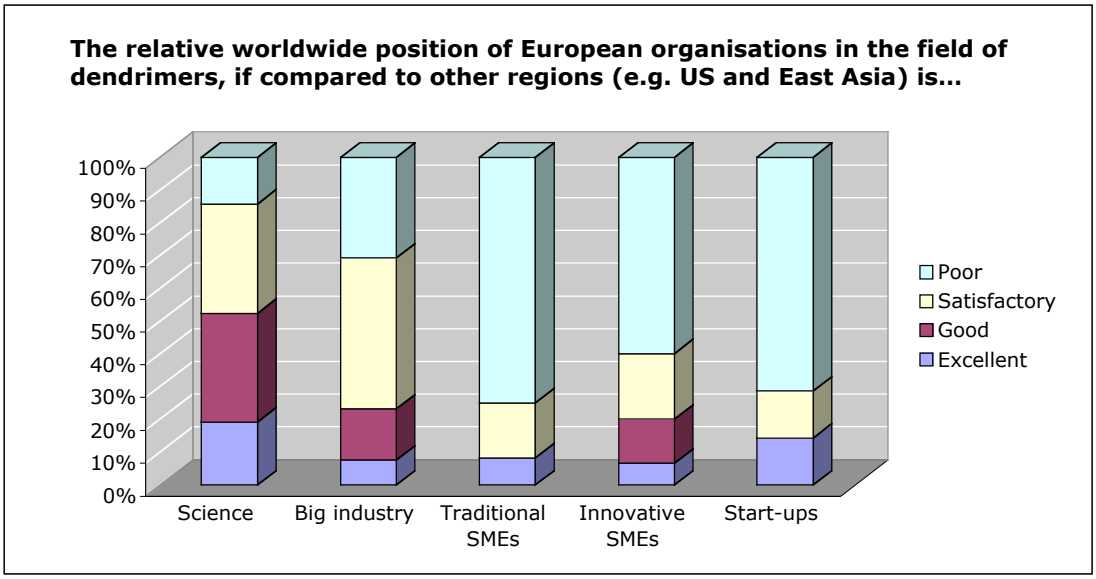
2.6.2 EU positioning in the field

Here, a clear distinction should be made between the academic and the industrial communities. The general perception is that European academic research in the field of dendrimers is of good quality. In fact, more than 60% of the participants in the Delphi panel think that it is either excellent or at least good.

The situation with European industry is considerably different. In this sense, only big industry has a satisfactory position, with less than 20% of the experts defining its situation as poor. Companies like DSM and Akzo Nobel (both from The Netherlands), Qiagen, Schering and Bayer (all three from Germany) and Perstorp (from Sweden) contribute to this perception.

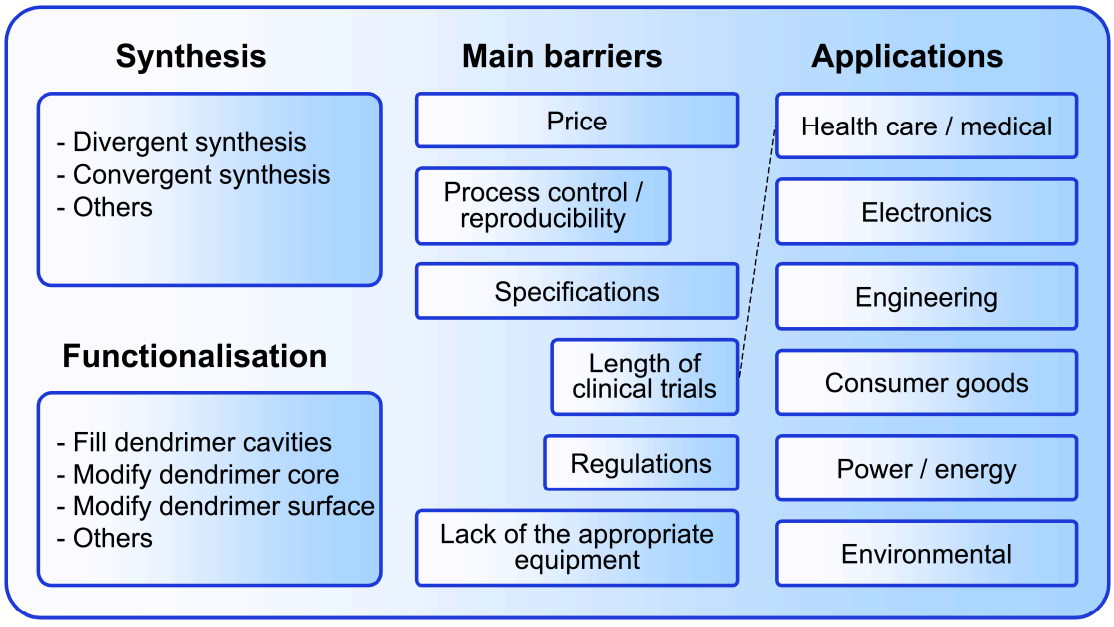
Both traditional and innovative SMEs and start-ups are poorly evaluated, with more than 40% of the experts defining their position as poor.

From a EU RTD policy point of view, this diagnosis by the experts leads to clear suggestion to focus RTD policy instruments above all on the link between academic excellence and industrial applications and competitiveness. Putting this assessment alongside the earlier statements regarding barriers to market it becomes all the more clear that industrialization is the key missing ingredient in EU dendrimer research and development. However, the way to achieve this varies greatly from one application to another.



2.6.3 Final conclusions and recommendations

The following figure summarises the most important barriers in the production and commercialisation of dendrimer related products.



Price is, according to the experts, the most important barrier in dendrimer synthesis and functionalisation approaches. However, this probably reflects the fact that most

current commercialisation is in materials domains where quantities can be significant. In upcoming medical applications, price is unlikely to be a major barrier. When considering materials applications, which still have great potential, substantial efforts should be put to reduce their price, whether through research on novel synthesis methods or through the reduction of steps in existing ones (combined convergent/divergent approaches can achieve this). If dendrimers are to be competitive against other materials / technologies in various applications such as those reviewed in this document, an important reduction of costs will be required, except in cases where dendrimers (or very similar macromolecular entities and methods) offer unique capabilities. Many of the biomedical applications fall into this category, with some exceptions where the landscape includes significant competitive technologies. MRI is the prime case of this and also targeted drug delivery, but to a lesser extent since dendrimers do offer unique capabilities over alternative such as nanoparticles or nanocapsules. And, as stated, volumes required in medical applications are generally small, leading to low price sensitivity. Upscaling of production is a key field of research for driving down costs in many applications. It may be an appropriate time for the production of dendrimers for many applications to come out of the labs and move into the pilot plants; such scaling initiatives should be applied mainly to new formulations with well-evaluated potential.

The evaluation of application/technology potential absolutely must consider the patent situation since the world of dendrimers is covered by many fundamental and applied patents in the hands of a few groups and individuals, and these groups have recently been forming patent agreements – see, for instance, the recent broad agreements between Dow Chemical (holder of earliest fundamental patents), Dendritic Nanotechnologies and Starpharma.

Note that scaling up of production does not necessarily mean the very large scales required for use in, say, composite fillers. Smaller level scaling can be valuable in areas such as biologically functionalised dendrimers. Additionally, an ability to rapidly produce new dendrimers templated to fit certain biomolecules and very rapidly scale up production could be one of the few defences against a newly evolved pandemic agent given that current responses, such as vaccine production, are notoriously slow and difficult to scale.

Another major potential barrier in the commercialisation of dendrimers for certain applications is problems with reproducibility. For some applications (e.g., medical, electronics, optical), it is key to work with high purity and well-defined products with reproducible properties. However, in terms of reproducibility, dendrimers fare far better than many other nanomaterials. Only in limited cases, the lack of more appropriate equipment can be considered a barrier to the success of dendrimers.

Reproducibility in electronic or optical applications will extend to the materials created with dendrimers where regular and consistent nanoscale organisation can be vitally important. This area would benefit greatly from improved modelling capabilities and the theoretical knowledge that feeds them, and the discipline of self-assembly will often be of particular relevance.

According to most experts, opportunities for dendrimer-related applications in the field of new therapeutic molecules are very broad. This report has mentioned many of the attributes of this wide range of applications, from targeted drug delivery to antiviral creams or biomolecular binding to fight toxins, various infectious agents, immunosuppressives and more. Targeted research, however, will require substantial

investment from national and EU governments and in this area a pool of capabilities also needs to be assured through extended basic research with dendrimers in the life sciences. This would be justified because, as the previous figure *Risk involved vs. expected market growth* shows, risks associated with these developments will, in the short term, be very high, but the range of potential benefits are huge. Once it becomes clear that there are a number of key medical uses for these capabilities, the pharmaceutical industry will be ready to take the next step and invest the necessary resources on its own.

Basic research should also be supported in the area of engineering macromolecular and supramolucular structures, for which dendrimers make an excellent tool. This is a long-term investment as the ultimate creation of nanodevices that will emerge is some way off.

Other barriers are application-specific. The medical field, for example, will have to face lengthy clinical trials in order to be able to commercialise dendrimer-based products. Other aspects that might influence broader application fields might be regulation and application-related specifications. Even though it could be tempting to ask for a global regulation involving all types of dendrimers, their chemical diversity and related properties are so broad that this would be unfeasibly complex. According to some sources, it would be easier to just use regulations classically applied to small molecules.

Annex I. List of participants (and statistics)

We would like to express our special gratitude for the collaboration of **Mr. Paul Holister** in the review of this document.

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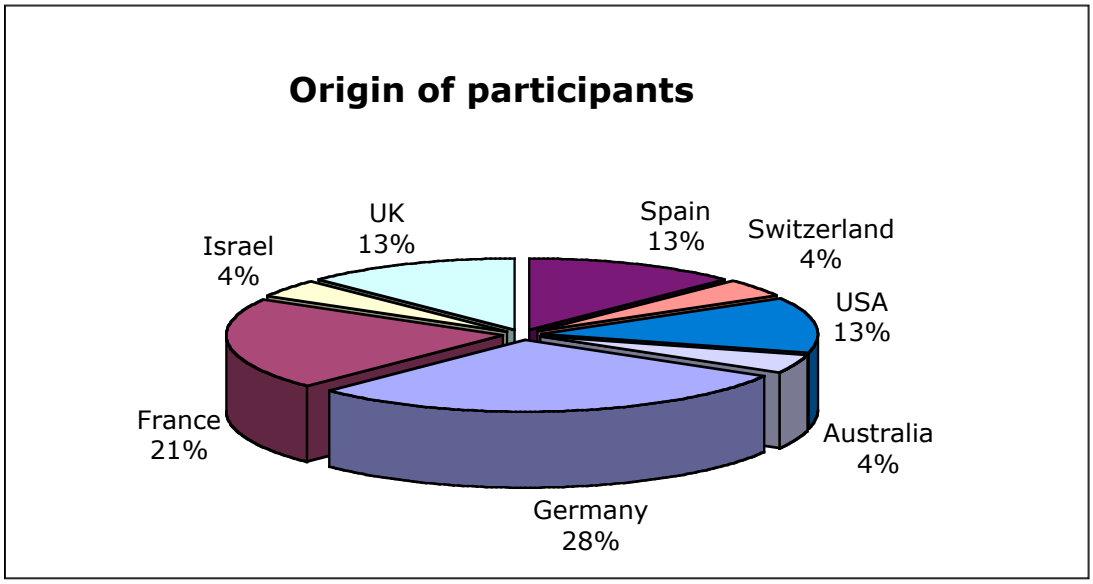
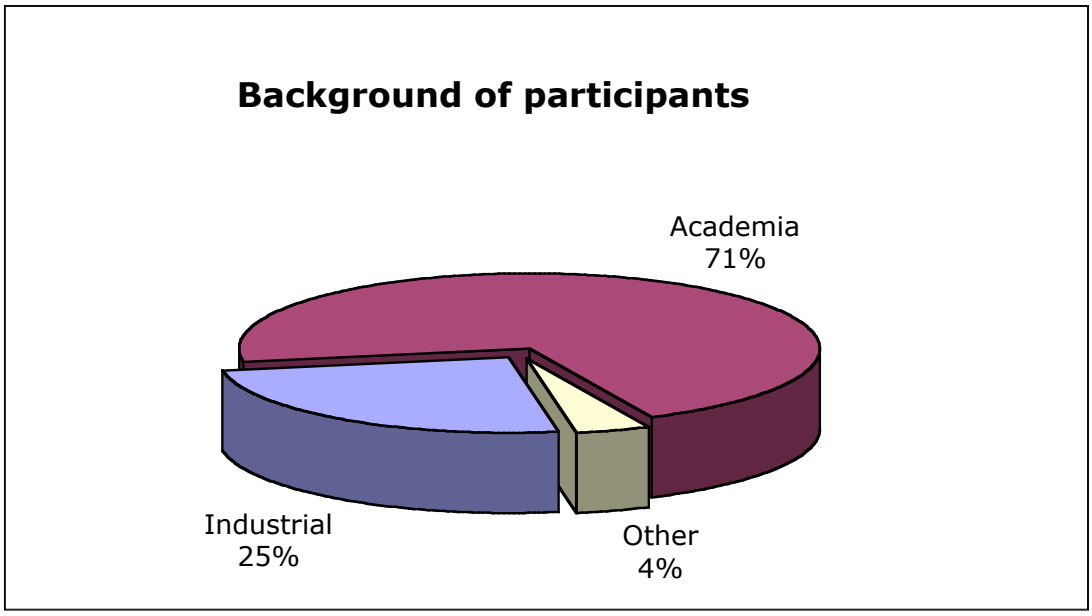
Director R&D
Germany


Origin of participants
UK
13%
Spain
13%
Switzerland
4%
Israel
4%
USA
13%
France
21%
Australia
4%
Germany
28%


Background of participants
Academia
71%
Industrial
25%
Other
4%

Annex II. Number of publications and patents