MSc Semester IV
16P4CHET14EL Advanced Organic Chemistry

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Dendrimers

- The word "***dendrimer***" originated from two Greek words,

  dendron :- meaning tree,

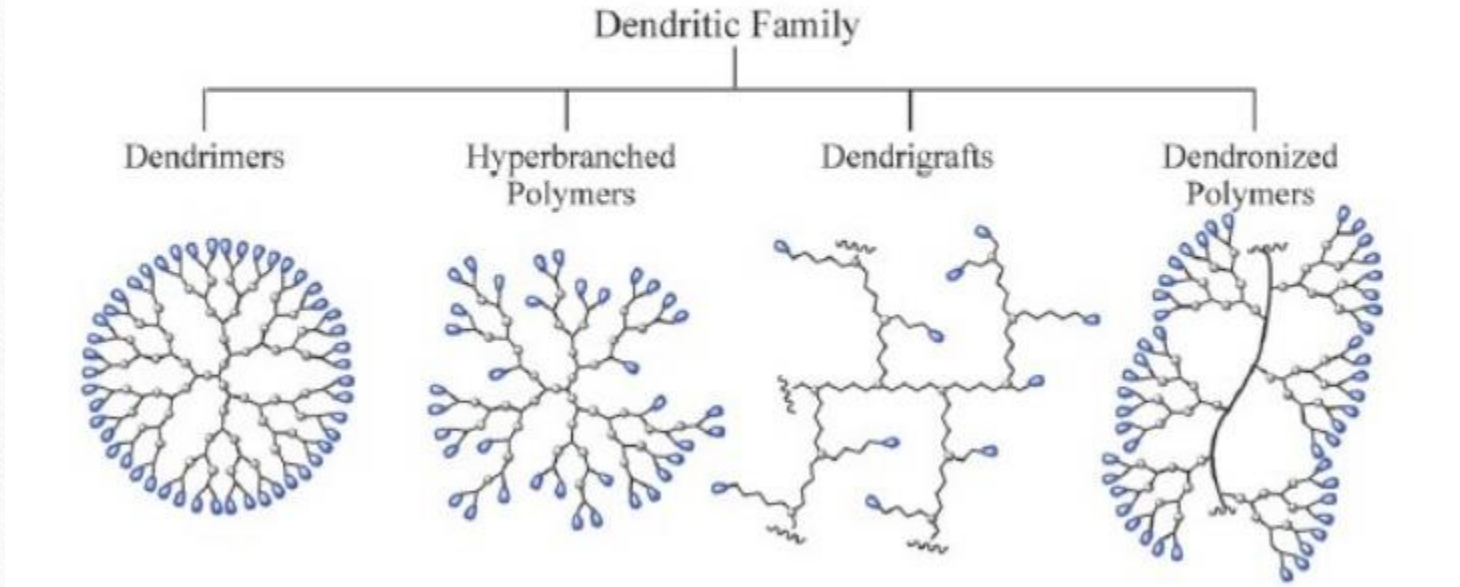
  meros:- meaning part or segment.

- Dendrimers are a new class of polymeric materials. They are highly branched, monodisperse , artificial macromolecules.
- Dendrimers may be defined as synthetic three-dimensional hyper branched, globular macromolecule, which is characterized by its highly branched 3D structure that provides a high degree of surface functionality.

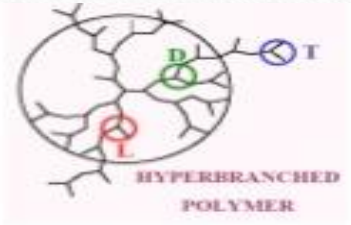
HISTORY

- In 1978, Vogtle and co-workers was first introduced chemistry of Dendrimer .
- In 1980, Donald Tomalia and co-workers discovered, these hyper branched molecules were called dendrimers.
- In 1985, Vogtle synthesized the first family of dendrimers the first "cascade molecules".
- At the same time, Newkome's group independently reported synthesis of similar macromolecules.
- They called them ***arborols*** from the Latin word 'arbor' also meaning a tree.
- The term ***cascade molecule*** is also used, but '***dendrimer***' is the well established one.

Dendritic Family



Dendrimers Vs Hyperbranched Polymers

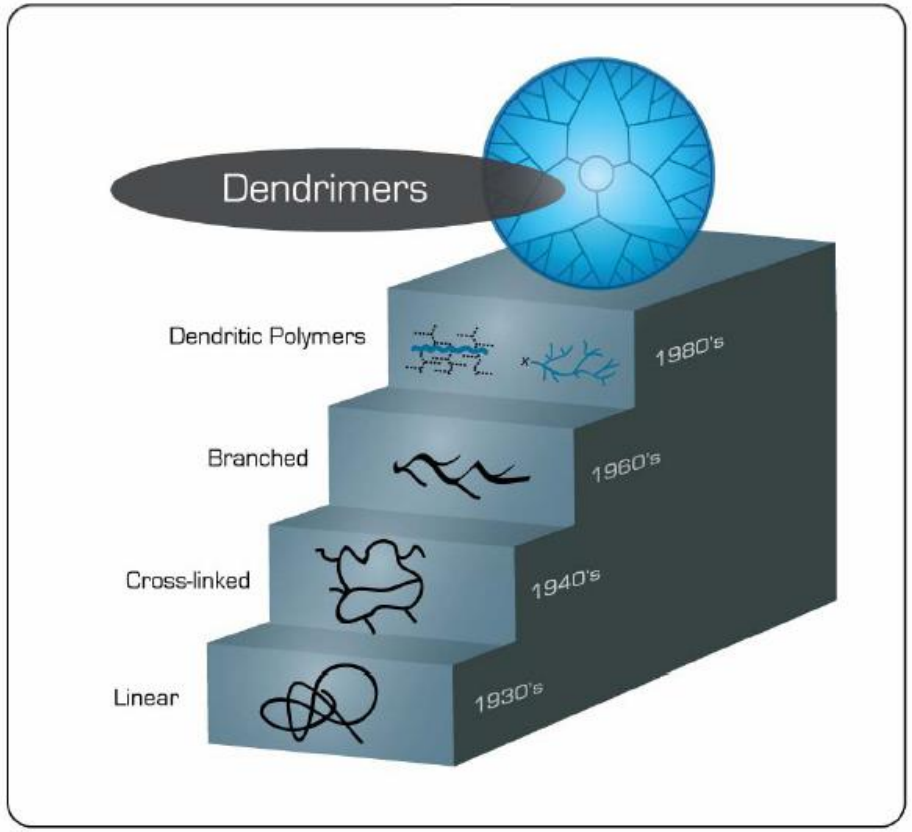


Dendrimers	Hyperbranched polymers
Dendrimers are highly uniform, 3-dimensional, monodisperse polymers with a tree-like, globular structure and a large number of functional groups With perfect molecular architecture.	*Hyperbranched polymers* represent another class of globular, highly branched macromolecules with a large number of functional groups. However, unlike dendrimers, hyperbranched polymers exhibit irregularity in terms of branching and structure.
Dendrimers are monodisperse [Degree of branching (DB) =1]	HBPs are polydisperse [DB<1]
Highly symmetrical in nature	Unsymmetrical in nature
Dendrimer synthesis requires absolute control over all the synthetic steps.	HBPs can be prepared by a one pot polycondensation process
The synthesis of dendrimer is quite tedious job and requires several protection and deprotection steps.	Easily synthesized by a one pot method
Final yield is very low so can not be applicable industrially	Final yield is high so can be synthesized in large scale

INTRODUCTION

- Dendrimers are a novel class of spheroid/globular nanoscaled macromolecules
- Characterized by highly branched tree like structers that provides a high degree of surface functionality &versatility
- Dendrimers are also referred to as the polymers of 21st century
- Due to their multivalent & monodisperse character,dendrimers have stimulated wide interest in the field of chemistry & biology, especially in applications like drug delivery, gene therapy & chemotherapy

DEVELOPMENT OF DENDRIMERS



STRUCTURE&COMPONENTS OF A DENDRIMER

A typical dendrimer is comprised of 3 different parts

- a focal core
- Building blocks with several interior layers (generations) composed of repeating units, radically attached to the interior core
- Multiple peripheral functional groups (end groups/terminal groups) attached to the outermost interior generations

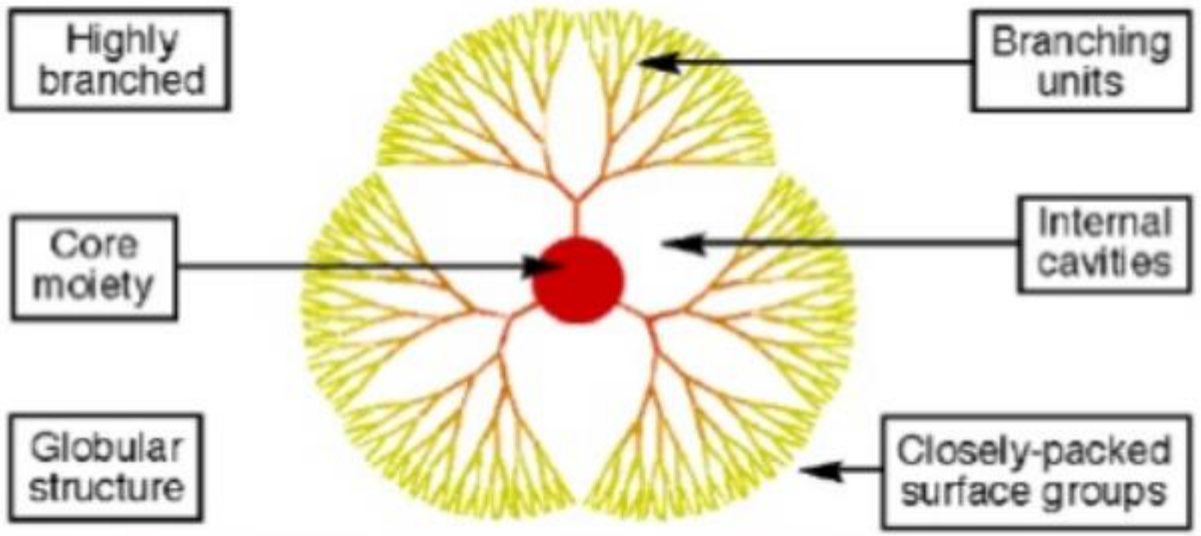
- Dendrimers possess three distinguished components, namely

(i) An initiator core.

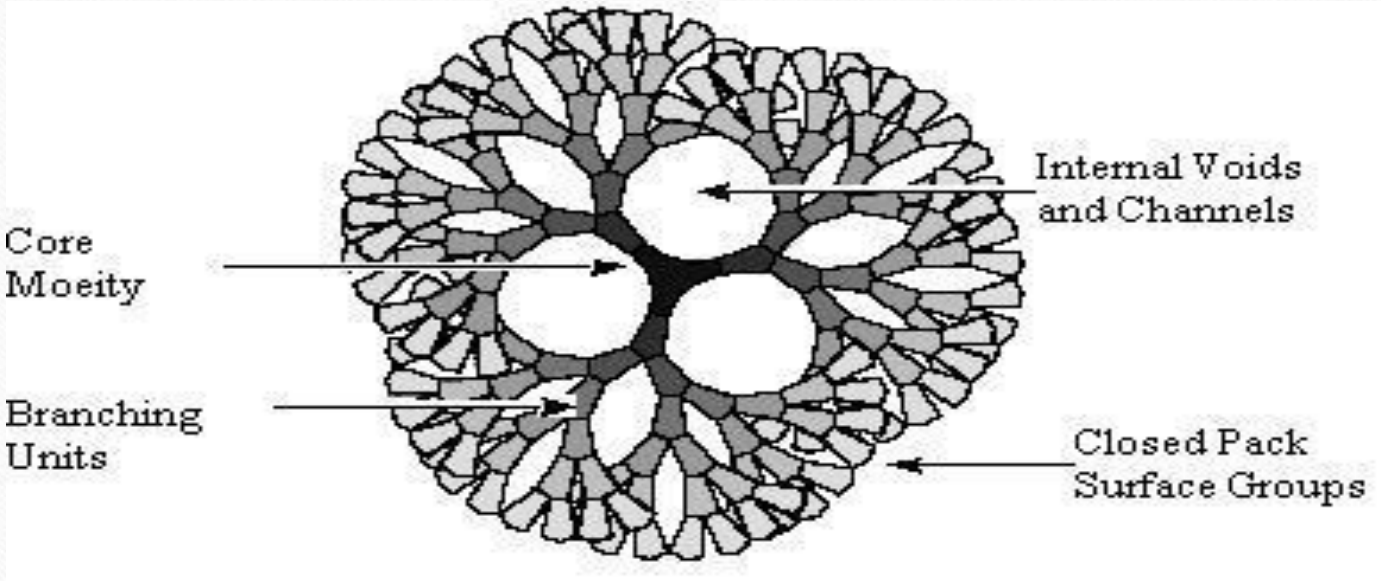
(ii) Interior layers:- composed of repeating units, radically attached to the interior core(generations).

(iii) Exterior layers :- attached to the outermost interior generations (terminal functionality).

The Dendritic Structure



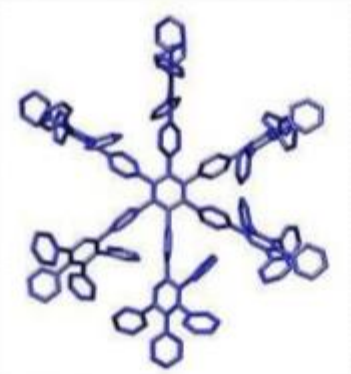
DENDRIMER STRUCTURE



TYPES OF DENDRIMERS

- Pamam Dendrimer
- Pamamos Dendrimer
- Tecto Dendrimer
- PPI Dendrimer
- Multilingual Dendrimers
- Chiral Dendrimers
- Hybrid Dendrimer Linear Polymers
- Amphiphilic Dendrimers Micellar Dendrimers

- ❑ Multiple Antigen Peptide Dendrimers
- ❑ Fréchet-Type Dendrimers
- ❑Glycodendrimer
- ❑Peptide dendrimer
- ❑Ferrocene dendrimer
- ❑Denderonised polymers



Fig;GLYCODENDRIMER

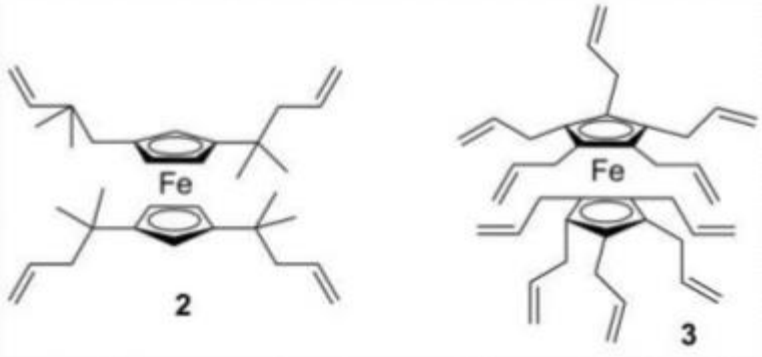


FIG: FERROCENE DENDRIMER

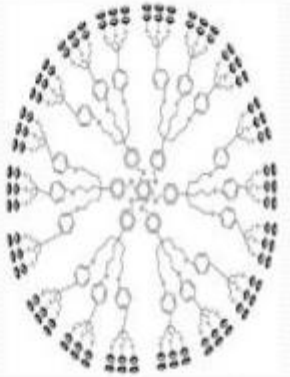


FIG:PAMAM DENDRIMER

TYPES OF DENDRIMERS

Pamam Dendrimer

- Poly (amido amine) dendrimers (PAMAM) are synthesized by the divergent method starting from ammonia or ethylenediamine initiator core reagents.
- PAMAM dendrimers are commercially available, usually as methanol solutions.
- *Starburst dendrimers* is applied as a trademark name for a sub-class of PAMAM dendrimers based on a tris-aminoethylene-imine core.
- The name refers to the star like pattern observed when looking at the structure of the high-generation dendrimers of this type in two-dimensions.

Pamamos Dendrimer

- Radially layered poly(amidoamine-organosilicon) dendrimers (PAMAMOS) are inverted unimolecular micelles that consist of hydrophilic, nucleophilic polyamidoamine (PAMAM) interiors and hydrophobic organosilicon (OS) exteriors.

- These dendrimers are exceptionally useful precursors for the preparation of honeycomb-like networks with nanoscopic PAMAM and OS domains.

PPI Dendrimer

- PPI-dendrimers stand for “Poly (Propylene Imine)”

- These dendrimers are generally poly-alkyl amines having primary amines as end groups, the dendrimer interior consists of numerous of tertiary tris-propylene amines.
- PPI dendrimers are commercially available up to G5, and has found widespread applications in material science as well as in biology.
- As an alternative name to PPI, POPAM is sometimes used to describe this class of dendrimers. POPAM stands for Poly (Propylene Amine)
- In addition, these dendrimers are also sometimes denoted “DAB-dendrimers” where DAB refers to the core structure, which is usually based on Diamino butane.

Multilingual Dendrimers

- In these dendrimers, the surface contains multiple copies of a particular functional group.

Hybrid Dendrimers Linear Polymers

- These are hybrids (block or graft polymers) of dendritic and linear polymers.

Amphiphilic Dendrimers

- They are built with two segregated sites of chain end, one half is electron donating and the other half is electron withdrawing.

Micellar Dendrimers

- These are unimolecular micelles of water soluble hyper branched polyphenylenes

Multiple Antigen Peptide Dendrimers

- It is a dendron-like molecular construct based upon a polylysine skeleton. Lysine with its alkyl amino side-chain serves as a good monomer for the introduction of numerous of branching points.
- **It** has predominantly found its use in biological applications, *e.g.* vaccine and diagnostic research.

Fréchet-Type Dendrimers

- It is a more recent type of dendrimer developed by Hawker and Fréchet**,**based on poly-benzyl ether hyper branched skeleton

❖ These dendrimers usually have carboxylic acid groups as surface groups, serving as a good anchoring point for further surface functionalisation, and as polar surface groups to increase the solubility of this hydrophobic dendrimer type in polar solvents or aqueous media.

Tecto dendrimer

❖These are composed of a core dendrimer, surrounded by dendrimers of several steps (each type design) to perform a function necessary for a s therapeutic nanodevice. Different compounds perform varied functions ranging from diseased cell recognition, diagnosis of disease state drug delivery.

METHODS OF SYNTHESIS:-

1) Divergent method.
2) Convergent method.
3) Hypercores & branched monomers method.
4) Double Exponential And Mixed Growth.
5) Other accelerated growth technique.

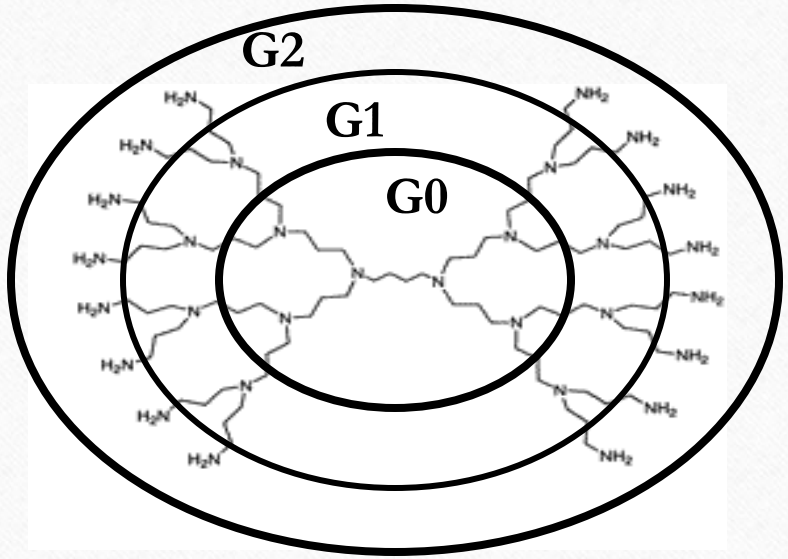
Synthesis of Dendrimers

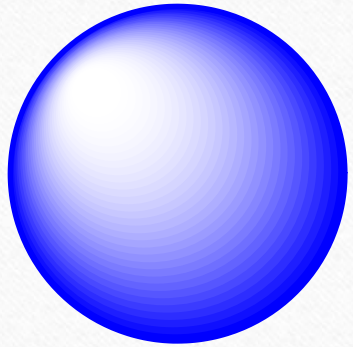
- Two major synthetic strategies used are
- Divergent method
- Convergent method

DIVERGENT METHOD

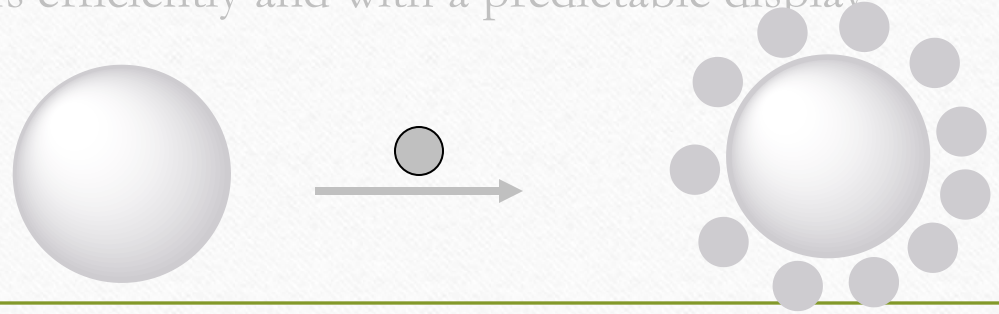
- Proposed by Tomalia & newkomes in the early 1980s
- Initiates growth at core
- Expands from in to out

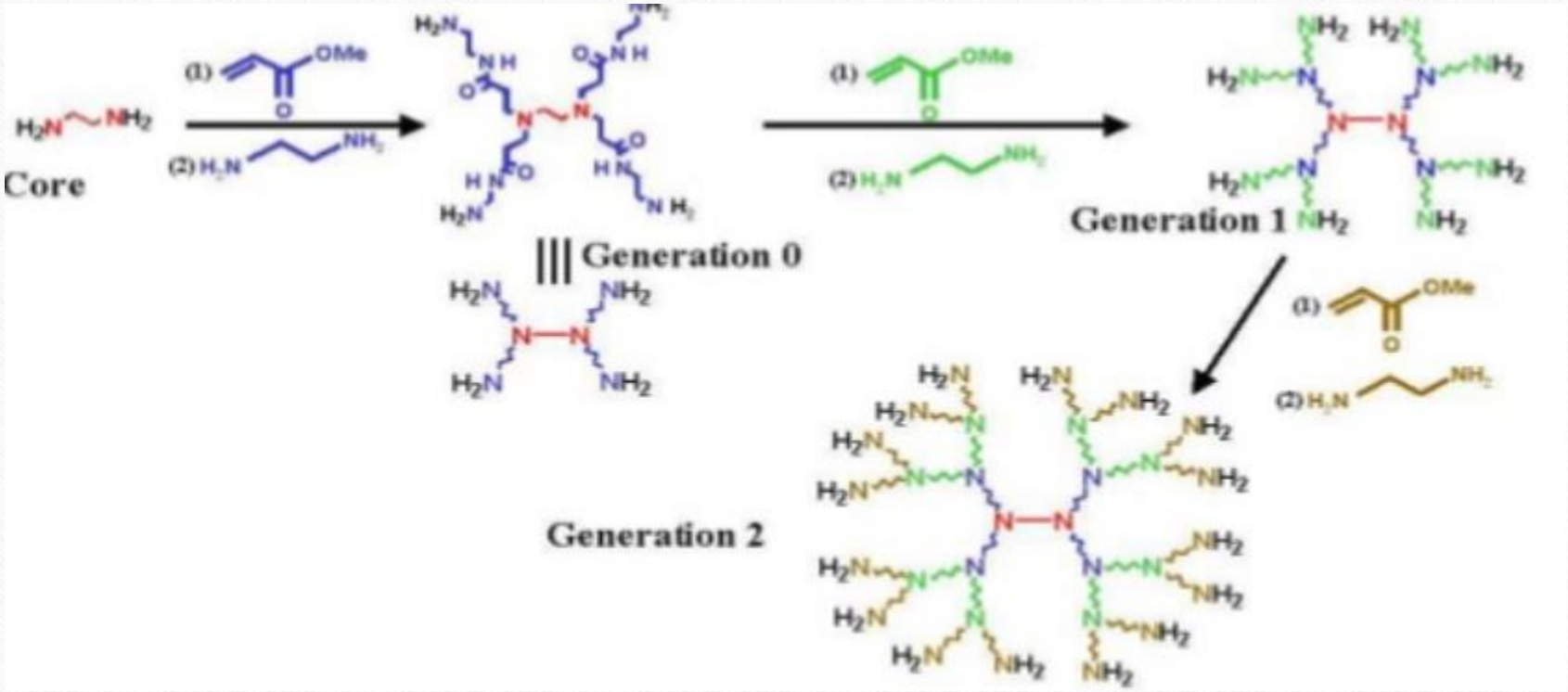
Generation (GX) Defines the level of branching within the dendrimer shell. At high **Generations** dendrimers become spherical





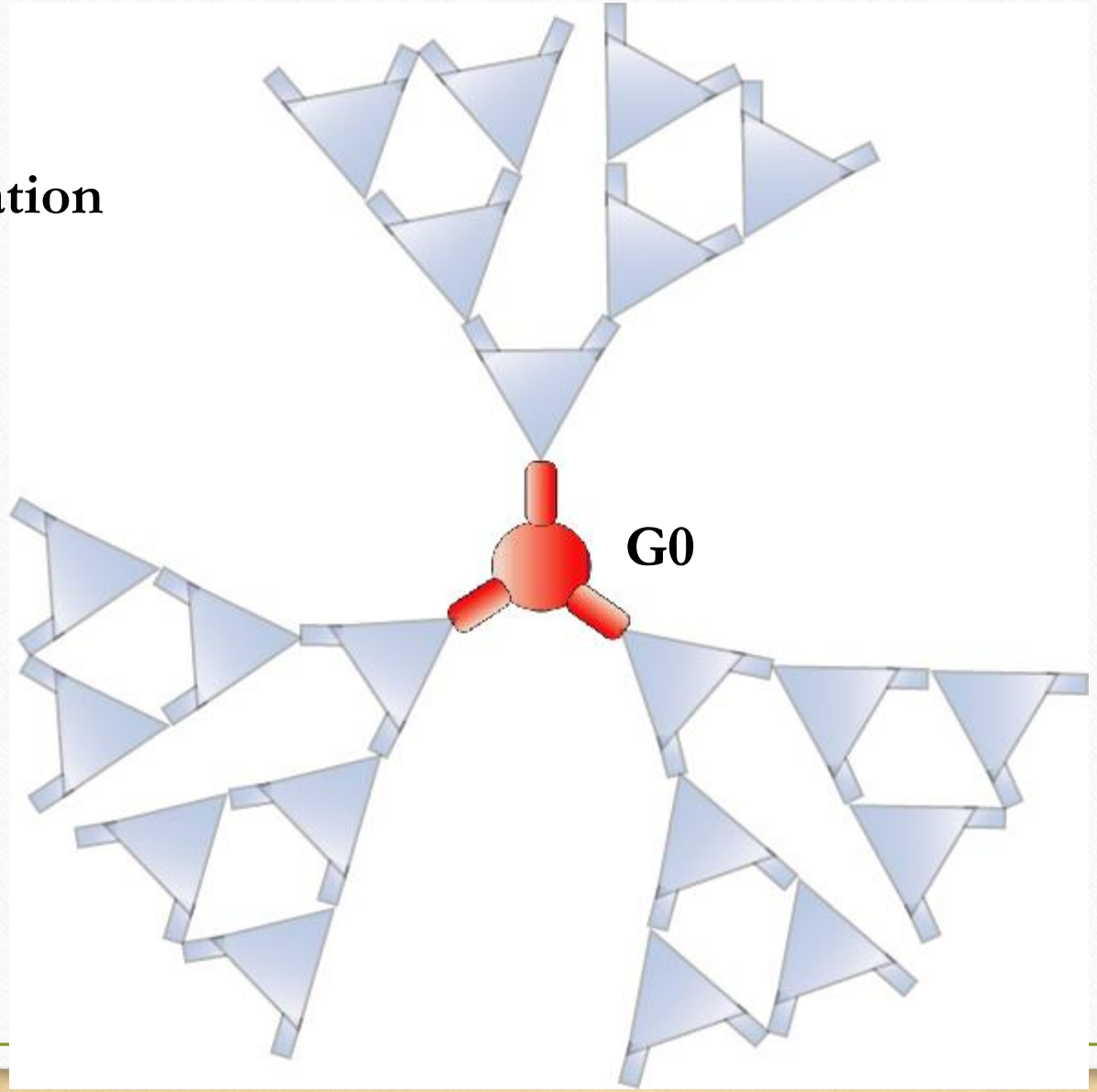
Loading Reactive/diagnostic groups can be attached to to the surface of the dendrimers efficiently and with a predictable display

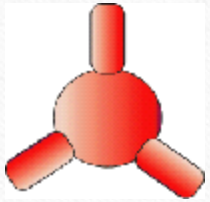



Core
(1)
OMe
(2)
Generation 0
Generation 1
Generation 2

Generation Growth

GX = generation



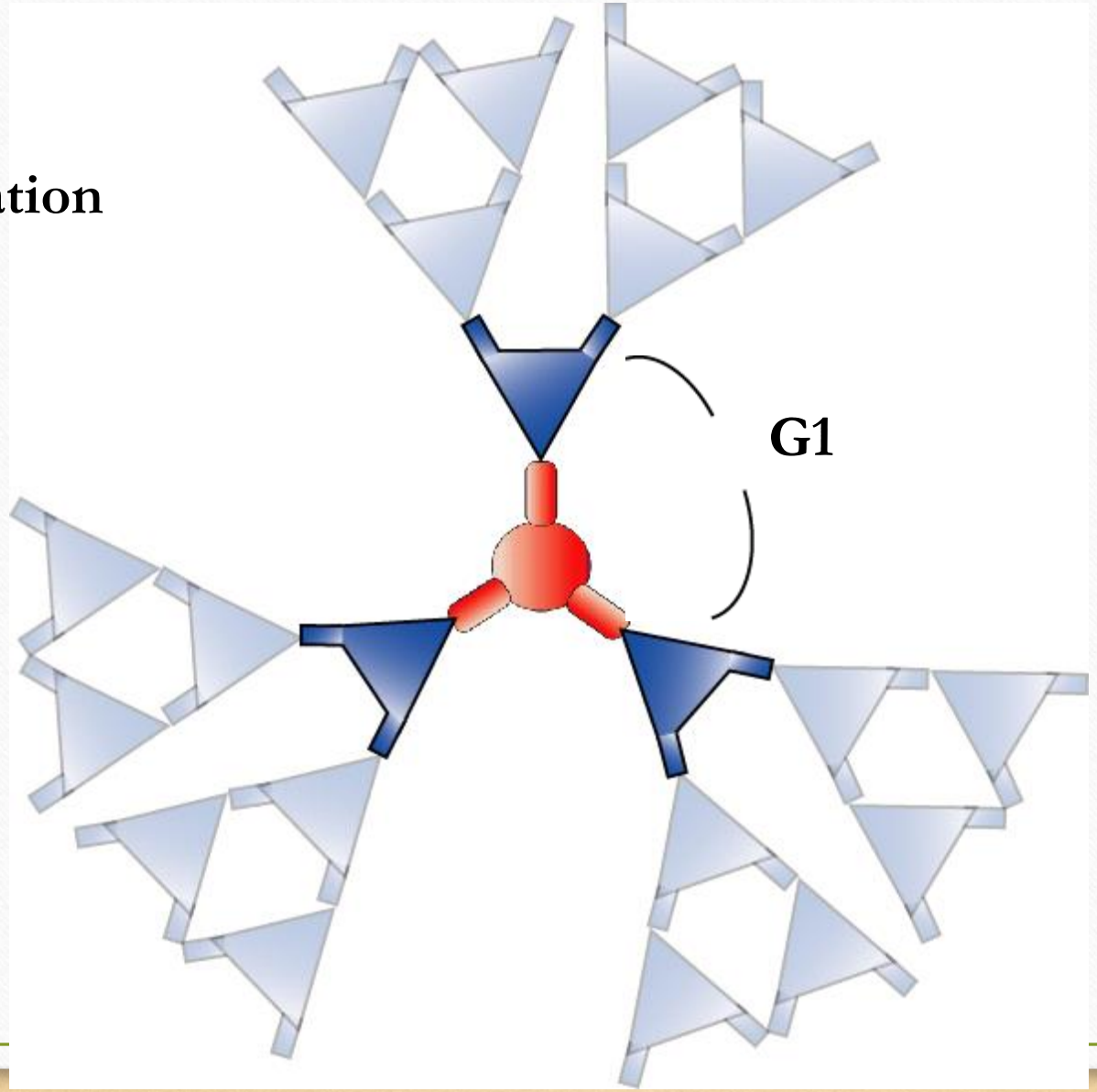


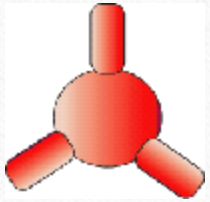
Core

Monomer

Generation Growth

GX = generation



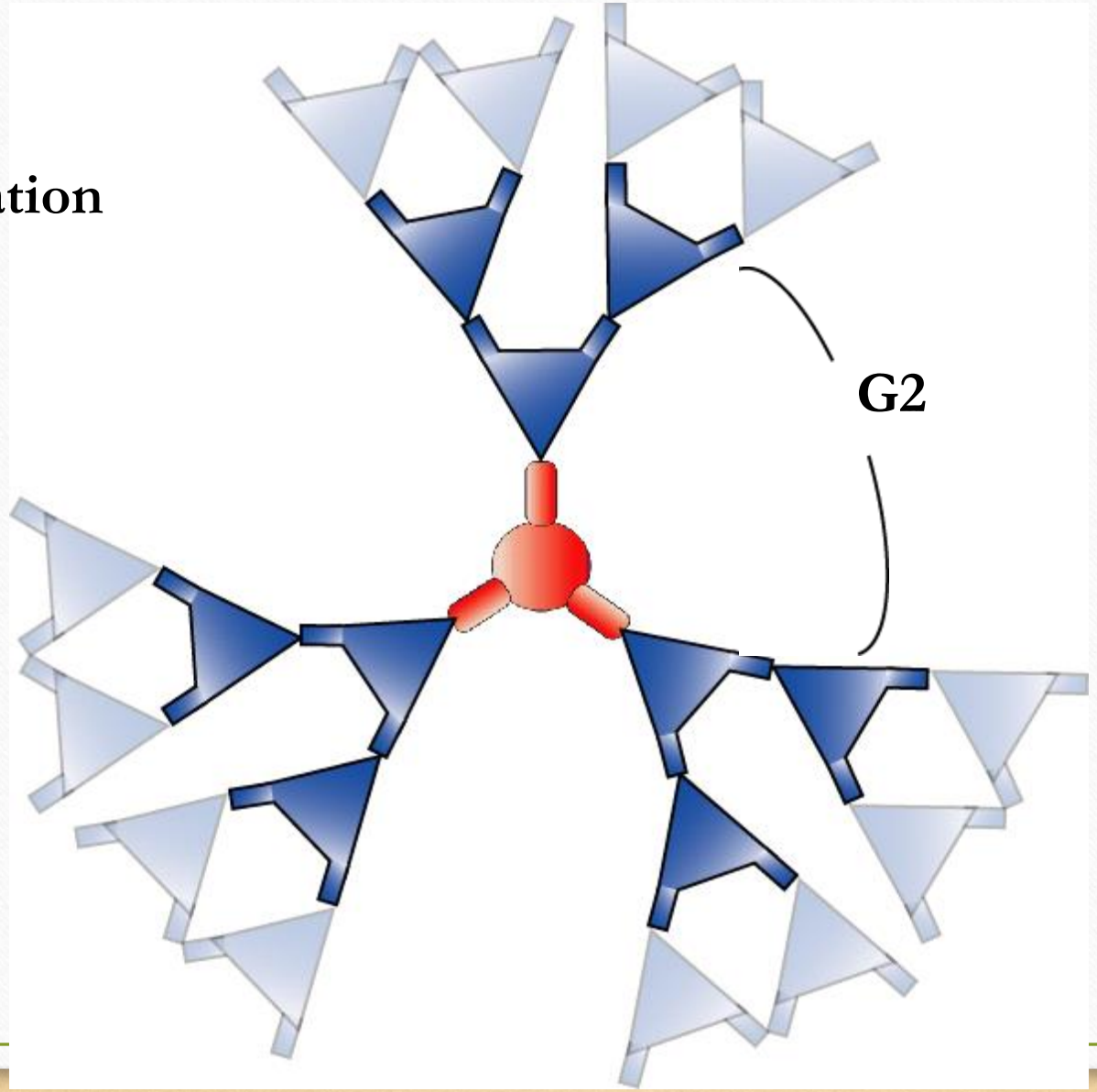


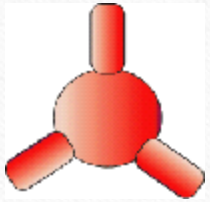
Core

Monomer

Generation Growth

GX = generation





Core

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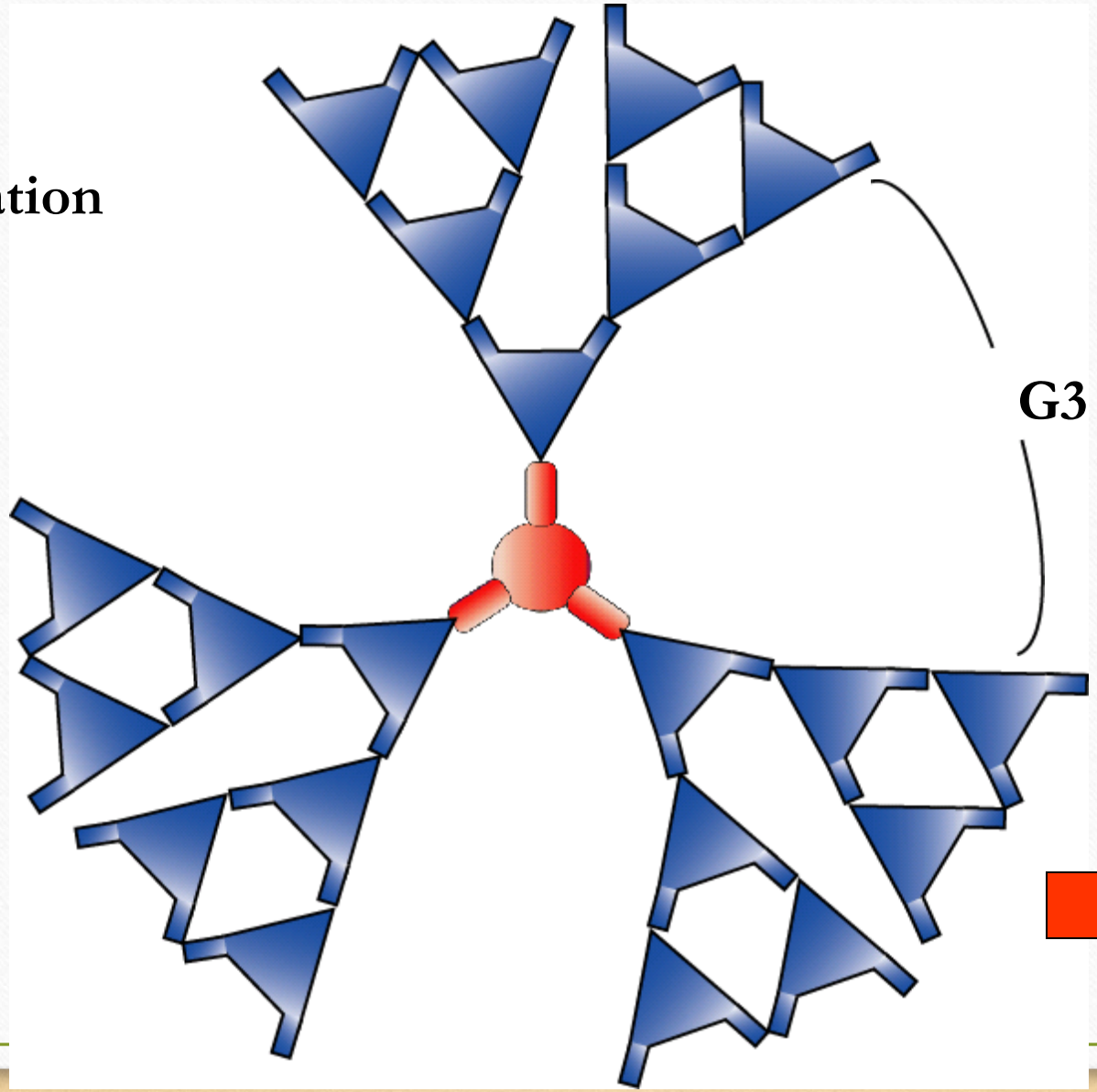
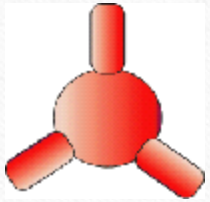
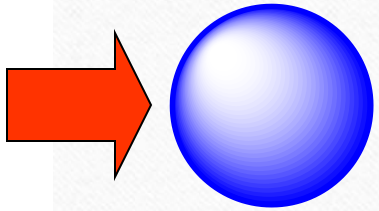




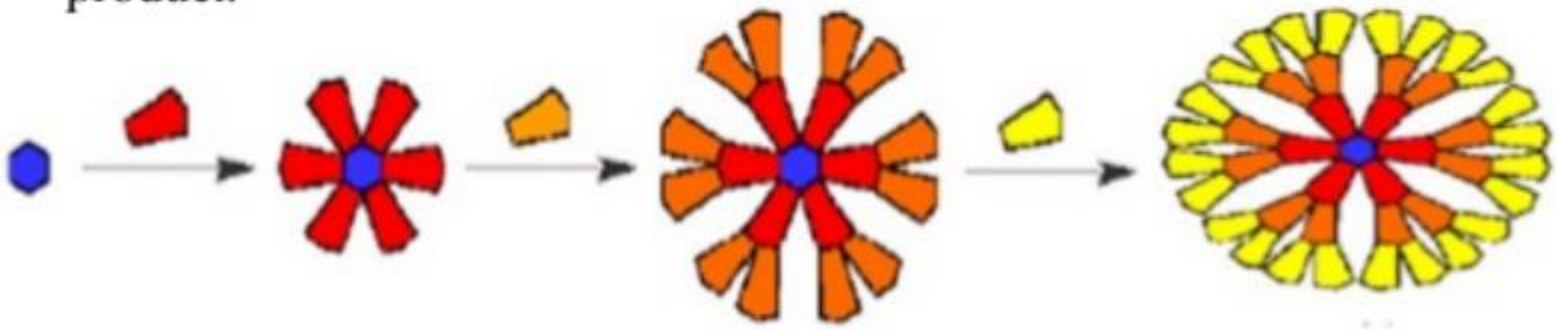
Core

Monomer

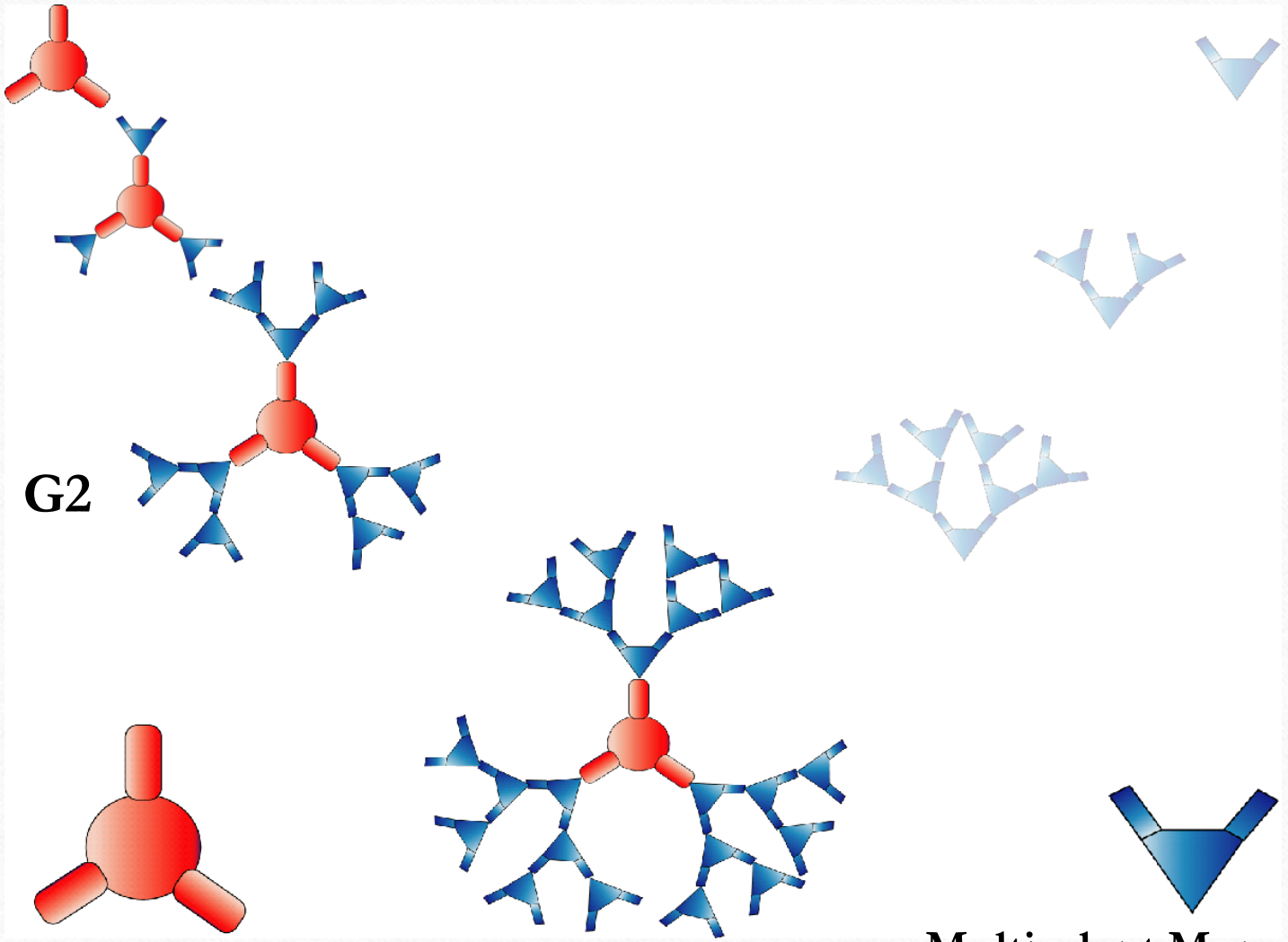


1) Divergent method

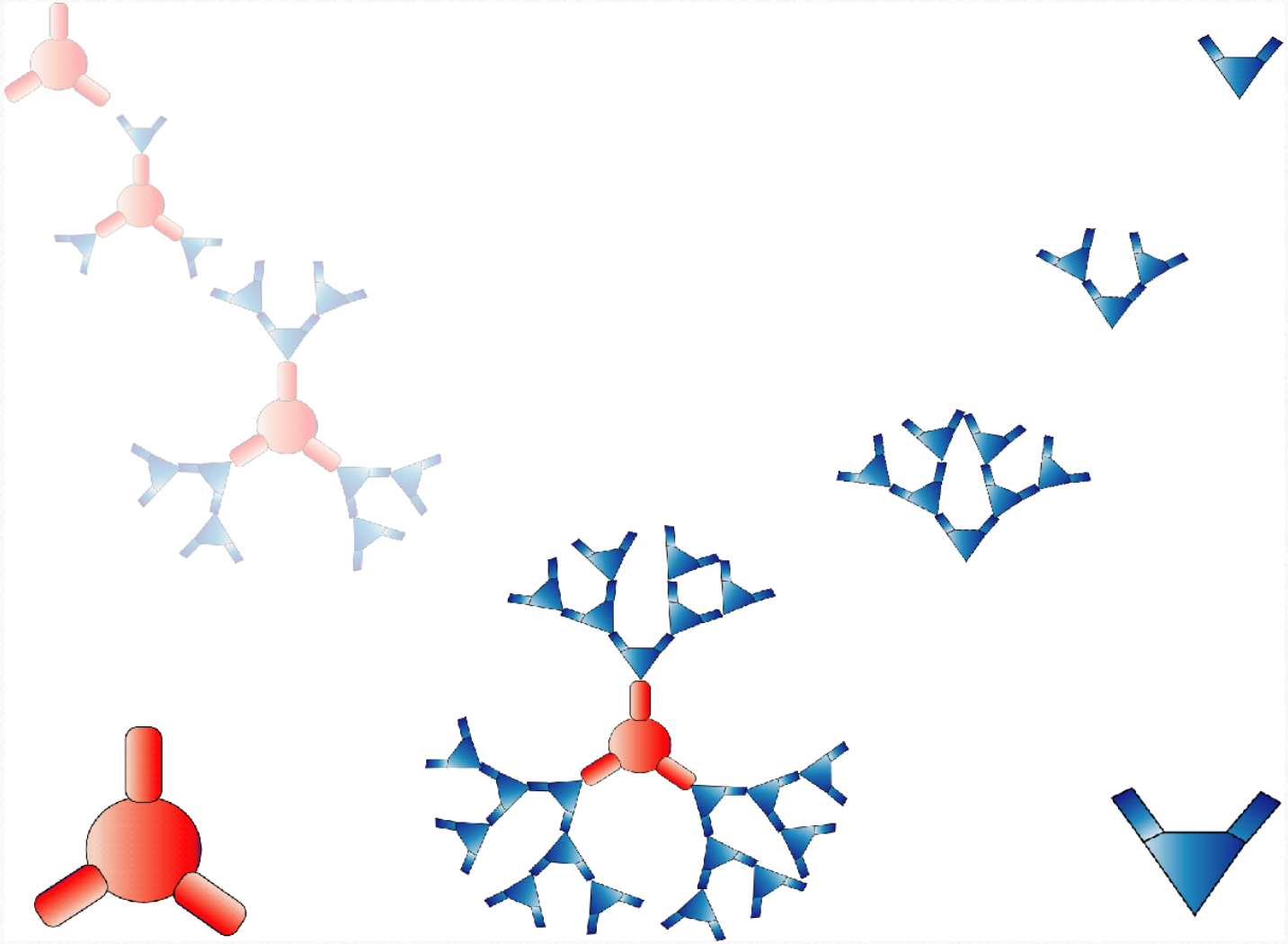
- Dendrimers starts from the central core and extends toward the surface i.e. diverging into space.
- Two step process:
  - Activation of functional surface groups
  - Addition of branching monomers units.
- Divergent approach is successful for the production of large quantities of dendrimers.
- It causes some difficulties in the purification of the final product.



Divergent Dendrimer Synthesis



Convergent Synthesis



Dendrimer Core **G3** **Multivalent Monomer**

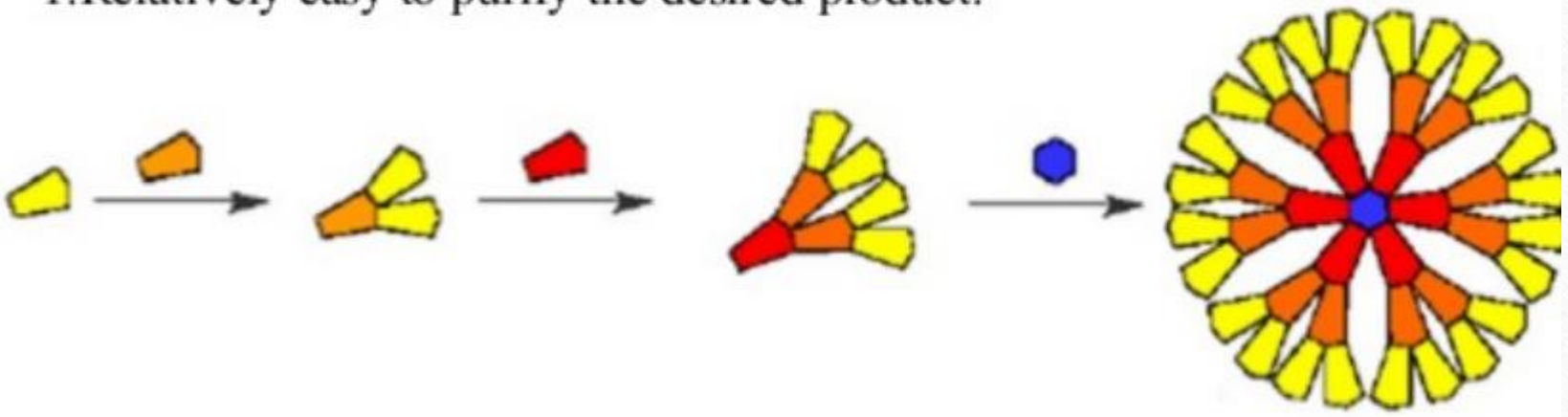
Hawker, C. J.; Frechet, J. M. J. *J. Am. Chem. Soc* **1990**, *112*, 7638-7647

2) Convergent method

- Dendrimer starting from the end groups and progressing inwards.
- When the growing wedges are enough large, attached to a suitable core to give a complete Dendrimer.
- The convergent methodology also suffers from low yields in the synthesis of large structures.

Advantages:

1. Relatively easy to purify the desired product.



Surface unit Monomers Core molecule Dendrimer

Synthetic Comparison

Divergent

Convergent

Advantages:

Rapid synthesis
Cheap reagents
Exponential growth
Large dendrimers attainable

Fewer simultaneous reactions
Standard purification
Intermediates characterizable
Differentiation
Monodisperse

Disadvantages:

Multiple side reactions (intra/inter)
Large excess of reagents
Low polydispersity

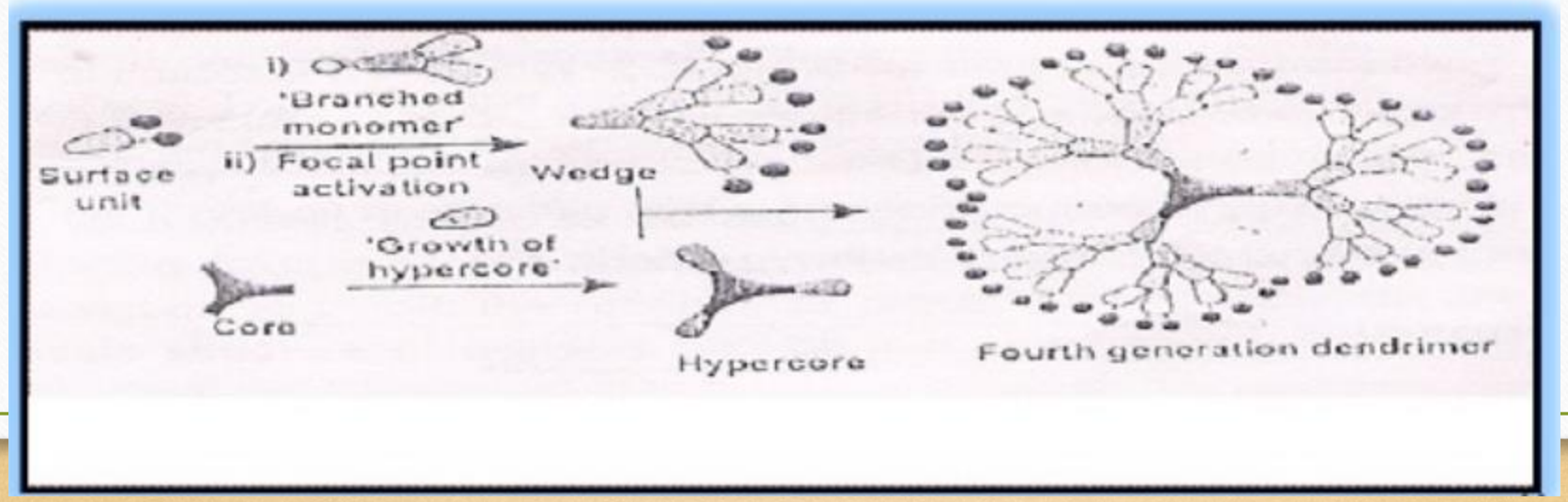
Slower growth process
Mid-sized dendrimers

3) Hypercores & Branched Monomers Technique

- Frechet group continued their efforts on research of hypercore & branchad monomers.

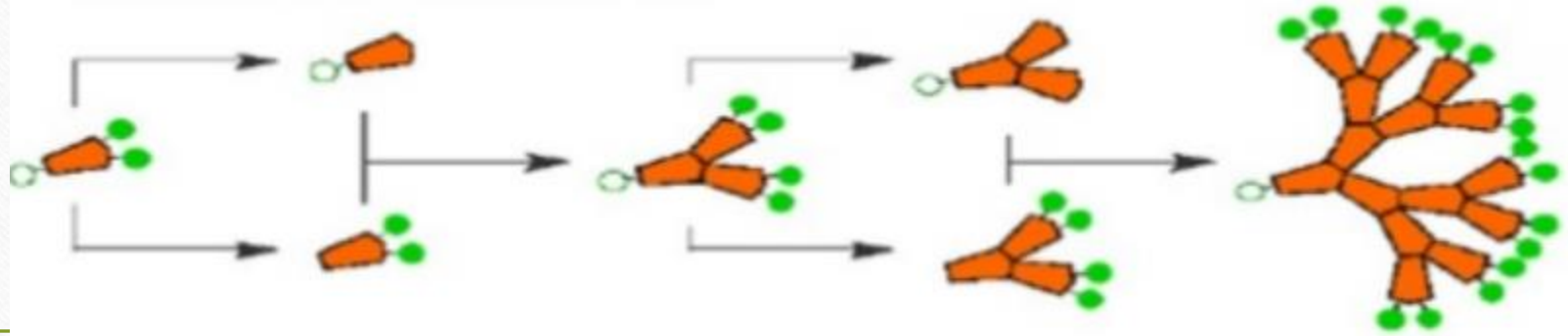
- This method involves the pre assembly of oligomeric species, which can then be linked together to give dendrimer.

- These monomers allow the to design synthetic strategies that are more convergent in classical synthetic sense of world.



4) 'Double Exponential' And 'Mixed' Growth

- Double exponential growth, similar to a rapid growth technique for linear polymers, involves an AB_2 monomer with orthogonal protecting groups for the A and B functionalities.
- This approach allows the preparation of monomers for both convergent and divergent growth from a single starting material.
- These two products are reacted together to give an orthogonally protected trimer, which may be used to repeat the growth process again.



5) Other Accelerated Growth Techniques

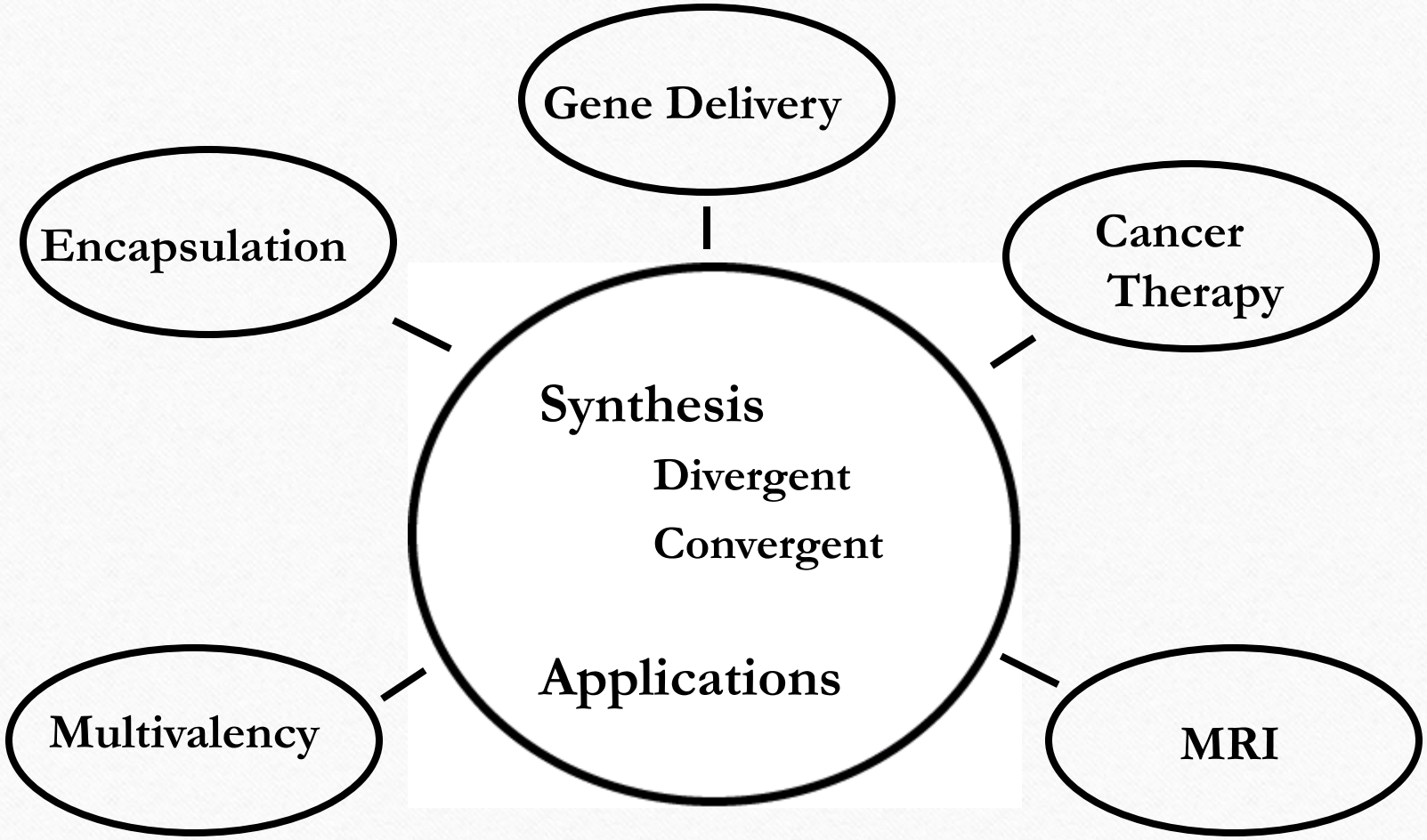
This is two step approach designed by frechet.

- In this approach two different monomers are used so as to avoid the need of an activation step between growth steps.

- The two monomeric units are AB2 &CD2.where A&D reacts to form bond under required conditions while B&C are stable, where B&C reacts to form bond while A&D remain stable.

- In this technique the hindrance likely to be experienced is that difficulty of finding a set of reactions,which conform to above criteria.

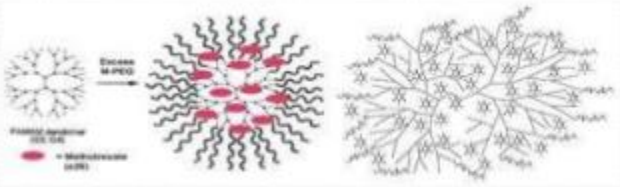
Outline


Gene Delivery
Encapsulation
Cancer Therapy
Synthesis
Divergent
Convergent
Applications
Multivalency
MRI

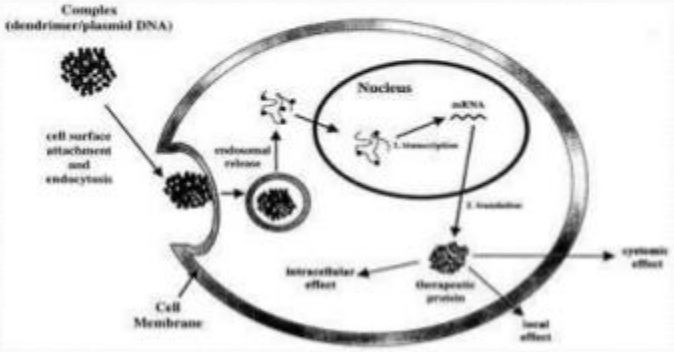
APPLICATIONS OF DENDRIMERS

❖PHARMACEUTICAL APPLICATIONS

- ❑Targeted And Controlled Release Drug Delivery
  - ➢Delivery of Anticancer Drugs
- ❑Dendrimer As Solubility Enhancers
- ❑Cellular Delivery Using Dendrimer Carriers
- ❑Dendrimers As Nano-Drugs
- ❑Dendrimers In Photodynamic Therapy



The encapsulation of anticancer drugs methotraxate (left) and 5-fluorouracil (right) into PEGylated generation 3 and 4 PAMAM dendrimers



Cellular delivery system

- Dendrimers In Gene Transfection
- Dendrimers in gene therapy
- Cardiac testing
- Boron Neutron Capture Therapy
- Dendrimers for Drug and Gene Delivery
  - Drug Delivery
  - Gene Delivery
  - Advancement in Gene Therapy
- Dendrimers in tissue engineering

Non-Pharmaceutical Application

- Diagnostics-MRI
- Dendritic Catalysts / Enzymes
  - Metallodendritic catalysts
  - Catalysis with phosphine-based dendrimers
  - Catalysis with (metallo)dendrimers containing chiral ligands
  - Non-metal containing dendrimers
- Industrial Processes

Mechanisms of Drug Delivery

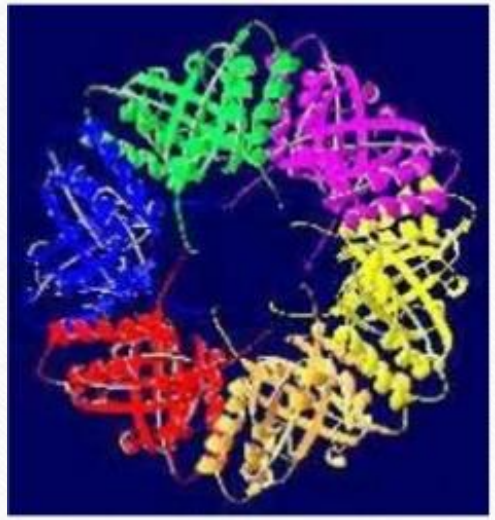
- **Simple encapsulation**:-It directly encapsulates guest molecules into macromolecule interior.

- **Electrostatic interaction**:-Surface functional groups enhances solubility of hydrophobic drugs by electrostatic interaction e.g. Ibuprofen, ketoprofen, indomethacin.

- **Covalent conjugation**:-The drug is covalently bound to dendrimers & its cleavage occurs via chemical or enzymatic cleavage of hydrolytically labile bonds. It allows tissue targeting & controlled delivery as drug-dendrimer conjugate diffuse slower than the free.

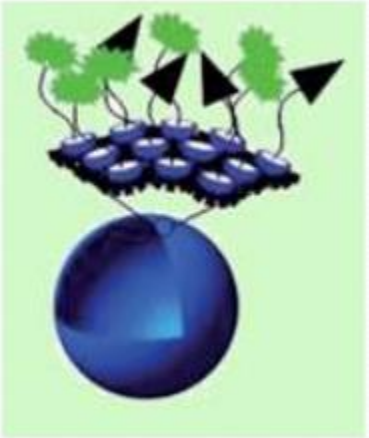
Nanocapsules

- Shell of polymer nanoparticles
- Held together by electrostatic forces
- Drug kept inside until released.



Benefites of Nanocapsules

- Receptors can be added without change to drug structure.
- Minimize drug degradation
- Increase drug bioavailability
- Dosage for drugs can be decreased by 10,000 folds.
- Ultra sound triggered release from capsules.



Nanocapsule shell creation

- The capsules may be sized according to the specifics of capsulated molecules
- Colloidal particles are used for structural support.
- Shell is assembled using nanolayers of different components and functions.
- Adjusting shell thickness controls permeability, stability and degradation time, ultimately resulting in control of release time.
- Biodegradable shells may be assembled from polysaccharides and polypeptides (approved by FDA).
  - Chitosan, alginate, dextran, and others polysaccharides.
  - Gelatin, polylysine, polyglutamic acid, albumin, and other polypeptides.