Article 8

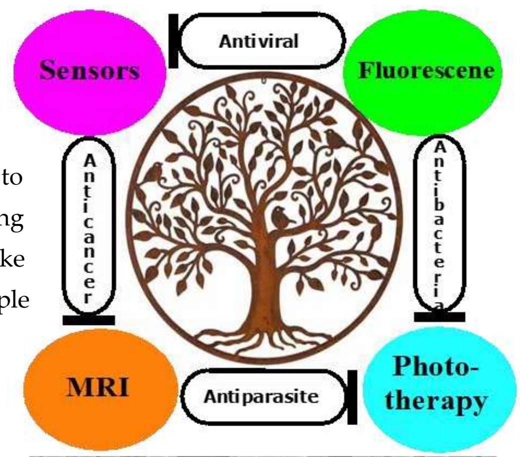
"Tree Like" Molecules in Biomedicine

A. Abd-El-Aziz and A. S. Abd-El-Aziz*

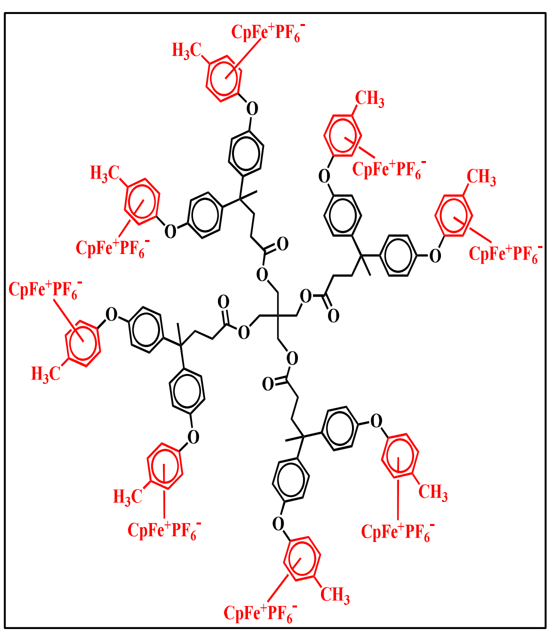
Qingdao Innovation and Development Center, Harbin Engineering University, China

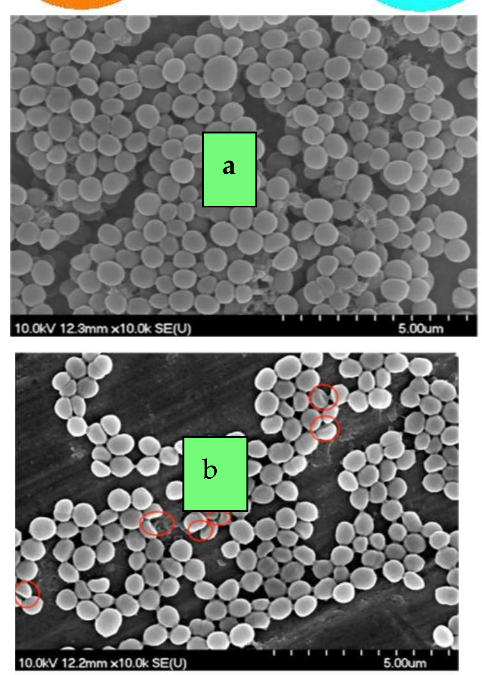
*Correspondence: alawork18@yahoo.com

Abstract:
This article gave a brief description to the field of dendrimers and their potential applications in biomedicine. It introduced dendrimers and identified the pioneers in this field of research. It also highlighted metal-containing dendrimers as antibacterial, antifungal, anticancer, anti-inflammatory and antiviral agents. The use of this class of dendrimers as sensors and in bioimaging was also included.



Dendrimer comes from the Greek word "dendron" meaning "tree". Dendrimers are macromolecules consisting of a small molecule or linear polymer core in addition to branches (dendrons) composed of a repeating unit and a terminal functional group. Like polymers, dendrimers can have multiple generations based on further addition of the repeating unit. Unlike linear or cyclical polymers, however, dendrimers more resemble a single molecule, as they extend outwards in three dimensions from a central point. The field of dendrimers is still quite



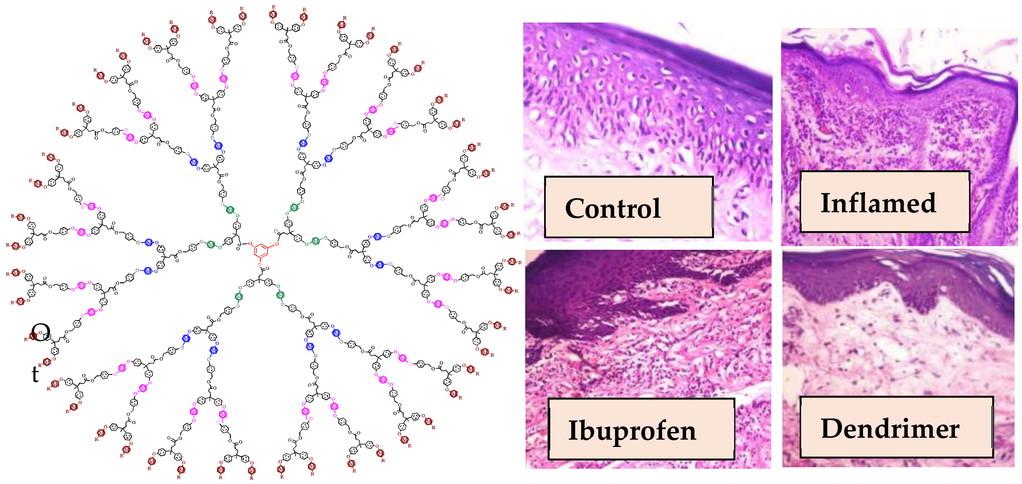


Reproduced from Ref. 10 with permission from the American Chemical Society, Copyright ©2015 young, as the earliest definitions of this class were described in the 1980s. Pioneers in dendrimers include: Fritz Vögtle, Donald Tomalia, George Newkome, Jean Fréchet, and Craig Hawker (Tomalia et al., 1985; Newkome et al., 1985; Hawker & Fréchet, 1990).

Didier Astruc and Alaa Abd-El-Aziz's research groups have examined the chemistry of transition metal-containing dendrimers and their application in biomedicine, catalysis, and nanotechnology (Astruc, 2012; Wang, Astruc, & Abd-El-Aziz, 2019; Abd-El-Aziz, 2020; Abd-El-Aziz, Agatemor, 2018).

The Abd-El-Aziz group examined many iron-containing dendrimers in combating various diseases, including cancer, as well as microbial and inflammatory diseases, for example, antimicrobial activities of iron-containing dendrimers against antibiotic-resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VRE), and *Staphylococcus warneri* (Abd-El-Aziz, Agatemor, Etkin, Overy, Lanteigne, McQuillan, & Kerr, 2015; Abd-El-Aziz, Agatemor, Etkin, Overy, & Kerr, 2015). The mechanism of action was through oxidative stress due to the generation of reactive oxygen species (ROS). High levels of ROS cause oxidative stress in cells that leads to cell death and is a useful mechanism to target cancer cells. The scanning electron micrographs of MRSA showed that, after treatment with dendrimer decorated with methyl groups at the IC50 (concentration necessary to inhibit 50% of growth), the bacterial membranes exhibited signs of rupturing and shrinking (b) that were not observed in the untreated bacteria (a). Another dendrimeric organoiron system containing a melamine core and piperazine moieties at the periphery had proven to yield effective antimicrobial agents. It was also observed that the higher generation dendrimer exhibited higher efficacy as the number of piperazine moieties increased (Abd-El-Aziz, Abdelghani, El-Sadany, Overy, & Kerr, 2016).

Organoiron dendrimers with aspirin or ibuprofen at the periphery showed anti-inflammatory activities. A rat model of inflammation was employed in which formalin was injected into the paw. As seen in the micrographs of rat paw tissue, the inflammation was reduced to near control levels by both ibuprofen and a dendrimer with ibuprofen at the periphery. The decreased inflammation was shown by lower cellular infiltration of white blood cells into the dermal layer, as well as decreased swelling and congestion of blood capillaries. These dendrimers also exhibited anticancer activities against breast, liver, and kidney cancer cells (Abd-El-Aziz, Benaaisha, Abdelghani, Bissessur, Abdel-Rahman, Fayez, & El-ezz, 2021; Abd-El-Aziz, Abdelghani, El-Ghezlani, Abou El-ezz, & Abdel-Rahman, 2021).



Other research groups have focused on other metal-containing dendrimers. As an example of antiparasitic activity, a ferroquine dendrimer has shown significant activity against malaria (specifically the species *Plasmodium falciparum*) compared to the control drugs chloroquine or artemisinin. The ferroquine moiety therefore allowed it to overcome the resistance to chloroquine (Khanye, Gut, Rosenthal, Chibale, & Smith, 2011). A series of copper-containing dendrimers were investigated for pre- and post-exposure therapy for HIV and were found to prevent binding of protein p24 to the cell in the initial infection step, as well as preventing HIV replication after the initial infection. Therefore, these dendrimers may be active against more than one stage of the HIV replication cycle (Galan, Sanchez-Rodriguez, Cangiotti, Garcia-Gallego, Jimenez, Gomez, Ottaviani, Munoz-Fernandez, & de la Mata, 2012).

Dendrimers have also been used to develop biosensors. An electrical biosensor using a platinum electrode coated with a dendrimer conjugated to transglutaminase proteins was designed for the detection of anti-transglutaminase antibodies found in patients with celiac disease. A linear correlation was observed with an increase in concentration of the antibodies, allowing for a calibration curve to be plotted for detection (Wilson, vam Wyk, Rassie, Ross, Sunday, Makelane, Bilibana, Waryo, Mapolie, Baker, & Iwuoha, 2015).

Bioimaging using dendrimers as fluorescence or contrast agents has been investigated. Further, dendrimers have been used for their application in phototherapy. Phototherapy uses lasers to target specific molecules in tumor tissue to either increase heat (photothermal therapy) or activate a photosensitizer drug (photodynamic therapy) to kill the cancer cells. Bioimaging can be used to both visualize the tumor for detection and then immediately use that information to target the tumor more accurately with phototherapy. An example of photothermal therapy was prepared using gold nanoflowers encapsulated with dendrimers and could use multiple forms of imaging including magnetic resonance imaging (MRI), computed tomography (CT), and photoacoustic imaging (PA). These dendrimer nanoflowers were also shown to be non-toxic unless stimulated with a laser (Lu, Li, Zhang, Peng, Shen, & Shi, 2018).

Future work

While significant progress was achieved in the development of organic and organometallic dendrimers, the field is quite young, and it is anticipated that there will be future discoveries in the design of new materials. There are unlimited possibilities in the incorporation of metallic moieties in the production of metallodendrimers with potential therapeutic activities that can meet the growing demands for production of antimicrobial, anticancer agents and other biomedical drugs as well as detection devices.

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