Journal of Research High School

Volume 2023 (1) 76 - 82
ISSN 2688-3651 [online]

Dendrimers and Cancer Therapy: A Review and Analysis

Alexander Xu[1,2,*], Emily Reynolds[1]

[1]Apex Learning Virtual High School, Richardson, TX USA
[2]Mountain View High School, Mountain View, CA USA

Received July 31, 2022; Revised January 5, 2023; Accepted, January 24, 2023

Abstract

Over the past two decades, dendrimers have emerged as a novel class of nanoparticles for cancer therapy and detection. They come in many varieties and are used to carry molecules like drugs or to act as imaging agents. They are composed of branches radiating out from a core, holding drugs between their branches or at the ends of them. Dendrimers are useful because of their customizability. They can be used for actively delivering drugs to tumors or for detecting cancer. Dendrimers have various traits that make them good for drug delivery, including their stability, water solubility, and uniformity. However, dendrimers also have limitations, displaying toxicity, or noting accumulate enough in the intended areas, and their interactions with the body are little known. Therefore, modifications to dendrimer structures are underway to solve some of the issues that their use presents. Overall, dendrimers show great potential in cancer therapy, but additional work needs to be done to enhance their specificity and effectiveness. They are important in the design of personalized cancer therapies, which we believe are the future of effective cancer treatment.

Keywords: Dendrimers, Cancer Therapy, Nanoparticle, Drug Delivery, Nanotechnology

1. Introduction

Cancer is a disease involving the rapid reproduction of mutated cells, often causing assorted physiological problems by disrupting organ functions. It is considered as the second largest contributor to worldwide mortality. The International Agency for Research on Cancer (IARC), an agency of the World Health Organization (WHO) projected around 29.5 million incidences and 16 million deaths by 2040. (Saluja, et al. 2021) Dendrimers are effective vectors for cancer therapy because they are compatible with the human body and because they are capable of delivering drugs or imaging agents to cancer sites and having a controlled release.

Dendrimers are nanoparticles ranging from 1 to 20 nm in size. The anatomy of dendrimers consists of branches radiating outwards from a core, with surface groups at the periphery. (Li, et al., 2017) Drugs can be stored inside the dendrimer between the branches, or attached to the edges outside the dendrimer. Their ability to be grown from scratch means that the structures of dendrimers are modifiable and more easily customized to suit one's needs. (Ruiz, et al., 2014) Dendrimers, while passively growable, can also be actively modified and rearranged. (Wolinsky and Grinstaff, 2008; Svenson, and Tomalia, 2012; Saluja, et al., 2021; Kumar, et al., 2020)

Dendrimes's solubility, uniformity and biodegradability make them ideal for drug delivery to cancer cells. Dendrimers typically enter cells via endocytosis. In cancer therapy, dendrimers see

* Corresponding Author
alexanderxu1111@gmail.com

Advisor: Emily Reynolds
Emily.Reynolds@edmentum.com

potential as imaging agents and drug delivery vehicles. They can migrate to tumors and allow them to be detected with machinery like X-rays. Additionally, they can be used to deliver drugs to tumors, thus killing them. Normally the release of drugs from the inside is hard to control, but this is solved via photodynamic or photothermal therapy in which certain kinds of light or heat act as triggers to release the drugs. (Wolinsky and Grinstaff, 2008; Svenson, and Tomalia, 2012; Saluja, et al., 2021; Kumar, et al., 2020)

Dendrimers have some issues, most prominently their toxicity, (Ruiz, et al., 2014; Kumar, et al., 2020) and solutions to this are still being worked on. Additionally, dendrimers are more prone to defects on larger scales and are not particularly effective at locating to and accumulating in tumors. (Saluja, et al., 2021; Bugno, et al.,2015) Currently, there are also not enough studies relating to long-term effects of dendrimers in the body, and their interactions with bodily systems are not well-understood. (Labieiec-Watala and Watala, 2015) This review focuses on the introduction of dendrimers and an analysis of their characteristics that make them good agents for cancer therapy.

2. Dendrimers

Dendrimers are well defined, nano-size, monodisperse, radially symmetric globular architecture having tree-like branching units. Their name is derived from the Greek words dendri- meaning ‘tree-like’ and meros meaning ‘part of’ (Kumar, et al., 2021). Dendrimers’ important characteristics make them promising in cancer therapy.

2.1 Types of Dendrimers and Dendrimer Anatomy

There are multiple kinds of dendrimers, including polyamidoamine (PAMAMs), Poly (propylene imine) (PPI), Poly-L-lysine (PLL), Core shell (tecto), hybrid dendrimers, and peptide dendrimers (Figure 1). They are small, radially symmetric, and consist of branches sticking out from a central core. (Wolinsky and Grinstaff, 2008) Their general anatomy consists of a core, branches, and an outside surface (Figure 2A). (Saluja, et al., 2021; Kumar, et al., 2020; Li, et al., 2017; Xu, et al., 2014)

Almost all dendrimers are capable of delivering drugs, and they all have their own up and downsides. Dendrimers deliver a variety of drugs, not restricted to but including cisplatin, doxorubicin, and various photosensitizing drugs. (Gillies and Fréchet, 2005) They can carry drugs inside them, sometimes with the help of hydrogen bonding (Svenson, and Tomalia, 2012) or drugs can be attached to the ends of the branches. (Saluja, et al., 2021) Dendrimer-drug conjugates are dendrimers with drugs on the ends, allowing multiple drug molecules to be attached to the ends of the dendrimer; and unlike drug-encapsulated dendrimers, the release of the drugs are controllable based on the linkages. (Wolinsky and Grinstaff, 2008) For cancer treatment, the most commonly used dendrimers are PAMAMs, PPI, PLL and Peptide drimers. (Saluja, et al., 2021) PAMAMs with ammonia/ethylene diamine as a core are a versatile tool due to their monodispersity. They are good at probing for cancer, as they immobilize DNA aptamers. (Li, et. al., 2017) AMAM-organosilicon dendrimers have PAMAMs on the inside and organosilicon peripherals. (Kumar, et al., 2020) PPIs are made of poly- alkyl amines inside and tertiary tris-propylene amines on the outside. They are hypothesized to be more effective at holding lipophilic drugs. Peptide dendrimers consist of a peptidyl core and peptide chain peripherals, and can be used for diagnosis as well as vaccine/gene delivery. Tables 1 and 2 show examples of dendrimer-based nanocarriers used for nucleic acid and drugs. (Palmerston Mendes L., et al., 2017)

2.2 Dendrimer growth and modification

Dendrimers are stable, capable of self-assembly, and polyvalent. (Kumar, et al., 2020) When grown, each activation and condensation reaction represents a step or a generation in which the number of surface groups doubles. (Bugno, et al., 2015) Figure 2B showed linear increase in diameter and exponential growth of the number of surface groups. (Xu, et al., 2014)

There are two main ways that dendrimers are grown: Either the dendrimer can be grown outwards

from the core (the divergent method), or the dendrimer can be grown inwards from the peripheral regions (the convergent method). (Wolinsky and Grinstaff, 2008; Saluja, et al., 2021)The larger a dendrimer is, the more spherical it becomes. (Kumar, et al., 2020) The amount of methods of growing dendrimers has led to over a hundred families and a thousand different surface modifications. () Two other emergent modifications include "Lego chemistry," which seemingly involves the use of pre-made cores and branches to create a dendrimer, as well as "click chemistry" which allows for the synthesis and isolation of dendrimers. (Svenson and Tomalia, 2012)

2.3 Dendrimer properties and development

Some key properties of dendrimers as nano-carriers of cancer drugs are being identified. Dendrimers are known for having a very controllable structure. (Li, et. al., 2017) Their "void spaces" between the branches are valuable because they allow the dendrimer to act as a transport vessel for drugs that are too insoluble to dissolve in the body by themselves. This is helped by the fact that the dendrimer itself is soluble. Additionally, they also help protect the drugs from destruction before they reach their targets. The ability for drugs to be stored within dendrimers allows for the development of controlled release methods that allow for more targeting precision. Dendrimers have a defined, uniform structure, which allows them to be reproduced and changed more easily. (Kumar, et al., 2020) They additionally are very small, being nanomaterials, making them better at crossing the cell membrane and reducing their clearance from the body. Dendrimers have long blood plasma retention time and are able to circulate for hours before being excreted, greatly influencing drug pharmacokinetics These properties of dendrimers make them ideal candidates for cancer drug delivery. (Saluja, et al., 2021; Kumar, et al., 2020)

Recently, dendrimers have progressed in development, and there are now some improvements being made to them. Modifying the charge of peripheral groups can help the dendrimer enter the body as well as help them spread throughout it. However, they cannot carry large amounts of drugs inside of them. Janus dendrimers are dendrimers with distinct groups on them that are different in terms of chemicals and structure, which can allow for the addition of multiple kinds of surface groups on one dendrimer or the higher loading of hydrophobic drugs, but in general drugs still have to be conjugated to be used inside of them; a similar problem that occurs with normal dendrimers. The merging of dendrimers with other nanocarriers has been proposed, in which dendrimers are put inside an even larger nanoparticle, leading to quicker circulation and better tumor accumulation. (Bugno, et al., 2015)

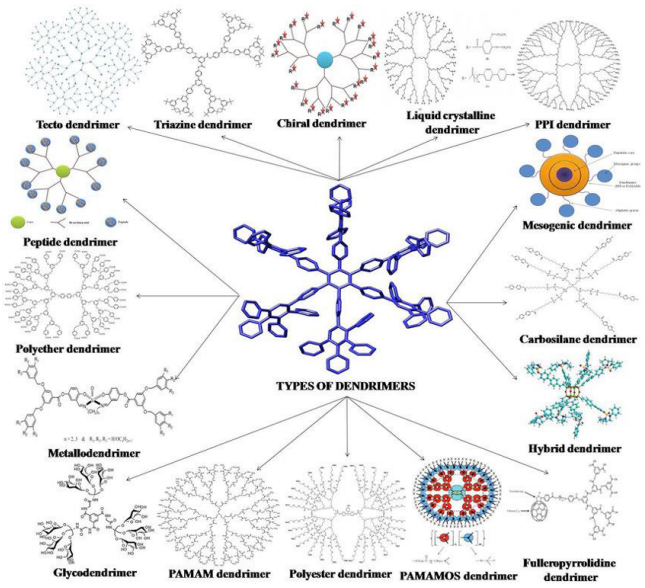

Figure 1. Major types of dendrimers. (Kesharwani, et al., 2014)

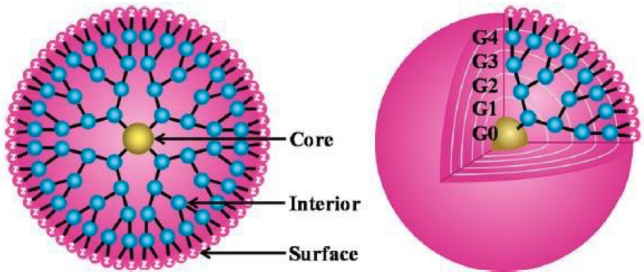

Figure 2. (A) Schematic presentation of dendrimers as a nanoscaffold with a core, interior branches and an outside surface (B) The growth of a dendrimer from its core. Abbreviations: G = generation; Z = surface group for host-guest interactions and functionalization. (Xu, et al., 2014)

3. Cancer Treatments and Detection

3.1 Dendrimers in cancer therapy

Dendrimers have been investigated extensively in the medical field, and cancer treatment is one of the areas where they have been most used. They are highly branched polymers with easily modifiable surfaces, which permits conjugation with drugs and DNA/RNA used for cancer therapy. (Palmerston Mendes L., et al., 2017) The drugs can be stored in the cavity of the dendrimers or conjugated to their functional groups at their surface. Nucleic acids usually form complexes with the positively charged surface of most cationic dendrimers (Table 1). On the other hand, folate and antibodies are often added as moieties on the dendrimer's exterior (Table 2).

Table 1. Examples of dendrimer-based nanocarriers for nucleic acids

Polymer	Generation	Payload	Application
PAMAM	G1	replicon mRNA	Vaccine
	G4	siBCL-2	Ovarian cancer
	G4	IFN-b	Malignant glioma
PPI	G2	pCN-Luci	LHRH positive cancer
	G3	siBCL-2	Lung cancer
	G5	siBCL-2	LHRH positive cancer
PLL	G3-G6	p-Luci	Gluconeogenesis
	G6	siGAPDH siOCT1	Gluconeogenesis
	G6	pCMV-Luc	Gluconeogenesis

Table 2. Examples of dendrimer-based nanocarriers for drugs.

Polymer	Generation	Payload	Application
PAMAM	G4	Doxorubicin	Lung metastasis
	G4	Paclitaxel	Breast cancer
	G4	Docetaxel	Breast cancer
PPI	G3-5	Melphalan	Breast cancer
	G4.5	Paclitaxel	Ovarian cancer
PLL	G6	Doxorubicin	Melanoma
	G6	Doxorubicin	Rectum cancer

3.2 Dendrimers in cancer drug delivery

In cancer therapy, dendrimers are intended to be used in order to deliver drugs used for different types of cancer. These drugs are either conjugated to the molecular structure of the dendrimer itself, or enclosed within the spaces between the branches of the dendrimer. (Wolinsky and Grinstaff, 2008) Targeted delivery of dendrimers to tumor cells prevents harmful side effects like toxicity.

There are two main kinds of targeting, passive or active. Passive targeting exploits the often inefficient or deformed properties of tumors, such as changed permeability of tumor blood vessels, which leads to the dendrimers naturally being absorbed and retained inside the tumors. Alternatively, active targeting involves the use of conjugation of targeting moieties to the dendrimer so that they can bind to the cell receptors of the cancer cells to enter. (Wolinsky and Grinstaff, 2008; Ruiz, et al, 2014) Scientists have studied the results of conjugating monoclonal antibodies, common cancer drugs, to dendrimers to target tumor cells that express certain antigens. For example, Human growth factor receptor-2 (Her-2) is often overexpressed in breast and ovarian malignancies. Shukla et al. showed that when an anti-HER2 was conjugated to G5-PAMAM and evaluated for binding affinities and internalization, it was found to specifically bind to HER2-expressing cells both in vitro and in vivo (Shukla, et al., 2006) It has been proposed that the shape of dendrimers gives them the ability to enter a cell via the cell membrane, but the more conventional method of entering a cell is through endocytosis. (Kumar, et al., 2020)

3.3 Dendrimers in photodynamic and photothermal cancer therapy

A major potential application of dendrimers is in photodynamic therapy, in which a photosensitizing agent is activated via light exposure and becomes toxic enough to cause cell death in tumors by generating reactive oxygen (Gillies and Fréchet, 2005; Ruiz, et al., 2014). Dendrimers have the potential to increase the efficiency of the photosensitizing agent's delivery, with the ideal dendrimer producing lots of singlet oxygen, no

toxicity when not exposed to light, high solubility, tumor targeting, and the ability to absorb light. (Klajnert, et al., 2012) Dendrimer- micelle complexes are especially effective, as they accumulate in areas prone to tumors and specifically target the vulnerable organelles of the cancer cells. (Wolinsky and Grinstaff, 2008)

Photothermal therapy operates in a similar way, except the dendrimers contain metal nanoparticles that heat up to lethal temperatures when exposed to light, killing tumor cells. (Wolinsky and Grinstaff, 2008) These strategies are very useful because they allow for complete control over drug release. (Ruiz et al., 2014) Boron neutron capture therapy is another option that uses boron-10's neutron capture reactions to cause localized cell death. (Kumar, et al., 2020)

3.4 Dendrimers in cancer detection

Dendrimers do not only have potential in cancer treatment, they may also be useful in cancer detection. By tethering fluorescent molecules to dendrimers, they can make their way to cancer cells, and their path can be tracked via fluorescence spectroscopy. Dendrimers with high molecular weights may make good MRI contrast agents. Their water solubility and stability also makes them good X-ray contrast agents, especially when iodine and barium are incorporate in CT and X-ray imaging, although the materials used could be toxic. (Kumar, et al., 2020)

3.5 Advantages of dendrimer drug delivery

Together with surgery and radiation, chemotherapy is one of the most commonly used cancer treatment options in the clinic. Chemotherapy drugs are frequently used for suppressing cancer cell growth, metastasis and disease progression. However, these drugs kill not only proliferating cancer cells but also normal cells. Other drawbacks include low solubility and bioavailability, short circulation time and nonselective biodistribution, which lead to unfavorable side effects. (Li, et al., 2017)

Compared to traditional drug delivery systems, dendrimers have shown greater potential in improving drug bioavailability, targeting tumors with specificity, prolonging drug circulation time and controlling drug release. Another major benefit to using dendrimers is the amount of control that they can be created with; as they have a modular and easily-modified structure (Ruiz, et al., 2014), which gives them lots of potential in drug delivery and cancer therapy. They are manipulable by changing the end groups and increasing generation, as well as modifying the mass of the components like the branches (Wolinsky and Grinstaff, 2008; Svenson, and Tomalia, 2012) and the potential diversity of forms means that it is easier to experiment with them until a desired result is reached. Additionally, they are uniform and have a well-defined structure; and as they are hydrophilic, they are also water- soluble. (Kumar, et al., 2020) They can be easily rebuilt. (Li, et al., 2017) Additionally, as multiple drugs can be placed on a dendrimer, they have a greater effect over other nanoparticles. Because drugs can be stored inside dendrimers or even in the core, they are shielded from the environment. (Klajnert, et al., 2012)

3.6 Disadvantages of dendrimer drug delivery and their solutions

Dendrimers have some drawbacks. First of all, there are some issues with the most commonly-used form of synthesis, divergent synthesis, which is prone to defects on larger scales. Larger dendrimers are more likely to have structural issues. (Bugno, et al., 2015) High generation dendrimers often have structural problems, although methods that fix this have been developed. (Saluja, et al., 2021)

Dendrimers can be quite toxic, especially large, catatonic ones due to their stability. (Ruiz, et al., 2014; Kumar, et al., 2020), and therefore harmful in large amounts, with surface groups often having to be modified to reduce toxicity and liver accumulation. (Gillies and Fréchet, 2005; Labieiec-Watala and Watala, 2015) They form holes in the lipid bilayer of cells; so the end groups should be capped to avoid injury to them. (Wolinsky and Grinstaff, 2008) Dendrimer interaction with blood is largely unknown, and few studies looking at the long-term effects of dendrimers have been carried out.

Drug-encapsulated dendrimers are difficult to

control, either releasing the drugs over several hours (Wolinsky and Grinstaff, 2008), releasing the drugs immediately, or requiring the dendrimer to face "harsh conditions" (Gillies and Fréchet, 2005), so they are most effectively used by injecting them directly into the tumor. Attempted solutions to the problem of controllability include the use of stabilizing polyethylene oxide chains or the hybridization of polyethylene oxide with dendrimers. Additionally, dendrimers do not accumulate in tumors enough, oftentimes with only 10% of the dose making it to its intended location. (Bugno, et al., 2015)

Photodynamic therapy also has issues, as photosensitizers can be toxic to important tissues and don't always target tumors specifically. α-lipoic acid (ALA) could be used to improve selectivity, but ALA moieties have been shown to increase the amount of toxic material generated inside tumors. The addition of micelles seemingly increases the amount of dendrimers accumulating in tumors, although they are ineffective at carrying drugs. Additionally, the opacity of skin makes sufficient light exposure difficult. The light penetration issue is being solved by lasers. (Gillies and Fréchet, 2005)

4. Conclusions

Dendrimers are continuing to be developed, built upon, and refined, with attempted improvements and new variations often appearing. The amount of control that researchers have over dendrimer structure, and thus function and usefulness, is a defining feature of dendrimers. (Wolinsky and Grinstaff, 2008) In recent years, there have been water soluble and biocompatible dendrimers created as well, which makes them far less harmful to healthy tissues and thus making it safer to use them to treat cancer. Their selectivity - only delivering drugs to cancerous tissues - would also give them an advantage over other cancer drugs. (Saluja, et al., 2021) They have so much potential in anti-cancer therapy because of their uniform size, distribution, and composition. (Ruiz et al., 2014) Photodynamic and photothermal therapy, as well as simply using dendrimers to deliver drugs, are all promising areas of research within the subject of using dendrimers in cancer therapy. Continued research in the area will bring macromolecules with increasing specificity and efficacy towards the diagnosis and treatment of cancer in the clinic.

In my opinion, the first major area to improve is specificity; as anything resembling a one-size-fits-all treatment is likely impossible due to the variety of cancers, variation of cancer microenvironment and difference in patients' response to different therapeutics. The most appropriate approach should be chosen based on individual cases and characteristics of each tumor. The multivalency of dendrimers is important in the design of personalized therapies. A customized dendrimer structure can potentially be tuned simultaneously for desired biocompatibility, bioavailability, drug circulation time, and targeted delivery of therapeutics to tumors. Efficacy could perhaps be improved with certain surface-level modifications, by finding a way to increase drug load, or by incorporating dendrimers into a more effective structure. In summary, there is no one technology that solves all issues. Instead, a patient-specific therapeutic agent would be required to achieve effective cancer treatment in years to come.

Acknowledgement

I would like to acknowledge Miss Emily Reynolds, who is my teacher and advisor for this independent research project. Her insights and support made the article possible.

References

Bugno, J., Hsu, H.J., & Hong, S. (2015) Tweaking Dendrimers and Dendritic Nanoparticles for Controlled Nano-bio Interactions: Potential Nanocarriers for Improved Cancer Targeting. Journal of Drug Targeting, 23(7-8), 642-650.

Gillies, E.R., & Fréchet, J.M.J. (2005) Dendrimers and dendritic polymers in drug delivery. Drug Discovery Today, 10 (1), 35-43.

Kesharwani, P., Jain, N. K., & Jain, K. (2014) Dendrimer as nanocarrier for drug delivery. Progress in Polymer Science, 39(2), 268-307.

Klajnert, B., Bryszewska, M., & Rozanek, M. (2012) Dendrimers in Photodynamic Therapy. Current Medical Chemistry, 19(29), 4903-4912.

Kumar, V., et. al. (2020) Diagnostic and therapeutic applications of smart nanocomposite dendrimers. Frontiers in Bioscience-Landmark, 26(3), 518-536.

Kumar, K., Singh, A., & Gupta, A. (2021) A role of dendrimers in drug delivery for cancer therapy. Int. J. Indig. Herbs Drugs, 1(6), 9–16.

Labieiec-Watala, M., & Watala, C. (2015) Dendrimers: Destined for Success or Doomed to Fail? Plain and Modified PAMAM Dendrimers in the Context of Biomedical Applications. Journal of Pharmaceutical Sciences, 104(1), 2-14.

Li, Z. et. al. (2017) Cancer drug delivery in the nano era: An overview and perspectives (review). Oncology Reports, 38(2), 611-624.

Palmerston Mendes, L., Pan, J., & Torchilin, V.P. (2017) Dendrimers as Nanocarriers for Nucleic Acid and Drug Delivery in Cancer Therapy Molecules, 22(9),1401-1420.

Ruiz, M.E., Gantner, M.E., & Talevi, A. (2014) Applications of nanosystems to anticancer drug therapy (Part II. Dendrimers, micelles, lipid-based nanosystems) Recent Patents on Anticancer Drug Discovery, 9(1), 99-128.

Saluja, V., et. al. (2021) Dendrimers based cancer nanotheranostics: An overview. International Journal of Pharmaceutics, 600(2021), 120485.

Shukla, R., et al. (2006) HER2 specific tumor targeting with dendrimer conjugated anti-HER2 mAb, Bioconjug. Chem. 17(1) 1109–1115

Svenson, S. & Tomalia, D.A. (2012) Dendrimers in biomedical applications—reflections on the field. Advanced Drug Delivery Reviews, 64(2012), 102-115.

Wolinsky, J.B., & Grinstaff, M. (2008) Therapeutic and diagnostic applications of dendrimers for cancer treatment. Advanced Drug Delivery Reviews, 60(9), 1037–1055.

Xu, L., Zhang, H., & Wu, Y. (20014) Dendrimer advances for the central nervous system delivery of therapeutics. ACS Chemical Neuroscience, 5(1), 2-13.