The Use of Dendrimers for Biomedical Applications

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Dendrimers are three-dimensional nanostructures with a high degree of molecular homogeneity, adjustable size, multivalence, high surface functionality, and high aqueous solubility. Due to these important and attractive properties, dendrimers are already being used to deliver a number of drugs and are being explored as promising carriers for nucleic acid-based vaccines. Here summarizes the literature data on the biosafety of some dendrimers has been evaluated in several clinical trials.

dendrimer drugs delivery safety and efficiency clinical trials

1. Introduction

Dendrimers are hyperbranched macromolecules composed of monomers radially emanating from a central core [1] (**Figure 1**). Due to their repetitive structure, dendrimers can be considered polymers, but in contrast to polymers, they are never synthesized by polymerization reactions, but step-by-step in an iterative fashion, creating layers. Each layer is called “generation” [2][3]. Higher-generation dendrimers (G > 3) have a near-globular shape [4].

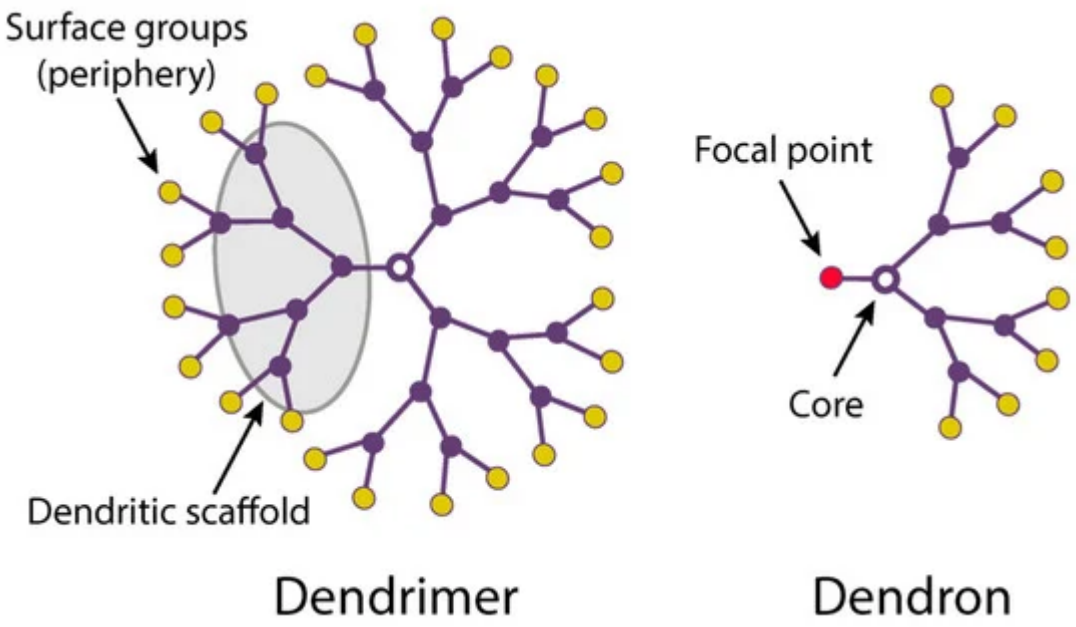

Figure 1. Schematic drawings of a dendrimer and dendron.

Owing to their peculiar synthesis, the structure of dendrimers is perfectly defined and highly reproducible. An isolated branch of a dendrimer is called a “dendron”. By choosing structural elements of dendrimers, one can opt for their physicochemical properties, adjust the molecular weight, functional group density, as well as modify dendrimers with different functionalities. The synthetic flexibility allows one to optimize their structure according to a specific task.

Dendrimers are a promising platform for designing functional species owing to their multivalency, which is reminiscent of the multivalent interactions widely found in nature. Multivalent interactions can be collectively much stronger than the corresponding monovalent interactions, in particular through multiple ligand–receptor interactions. Dendrimers, which are inherently multivalent species, are widely used in different fields of science and technology, such as catalysis [5], biomaterials [6][7], regenerative and cell biology [8][9][10][11], and nanomedicine [12][13][14][15].

One of the most intriguing properties of dendrimers and dendrons is the so-called “dendritic effect” [16], i.e., a dramatic increase in efficiency when using a dendrimer compared to monomer. The dendritic effect is influenced by the nature and size of the core as well as by the cooperativity of functional groups at the periphery. The dendritic effect-enhanced multivalency and structure uniformity are the major differences between dendrimers and hyperbranched polymers. They frequently define the dendrimer properties and behavior in different processes at the nanoscale level.

Apart from dendrimers, the use of dendrons is considered highly promising. Unlike dendrimers, dendrons have two topologically and chemically different sites: the focal point and the periphery, which enables their selective functionalization with various moieties, depending on the desired application. Such a feature allows dendrons to exhibit enhanced functionality compared to that of dendrimers. Today, dendrons have been applied as agents for imaging, catalysis [17][18][19], healthcare [20][21][22][23][24], nanoparticle stabilization and functionalization [25][26][27][28][29], surface modification [30][31], etc.

Amphiphilic dendritic species are an emerging class of dendrons holding great potential in a wide range of applications. By varying the nature and the structure of a functional moiety in the focal point, one can achieve the controllable self-assembly of dendrons into supramolecular associates [29][32][33][34]. Such molecules, which are in fact Janus-type particles, expand the functionality of dendrimers for various applications. For instance, amphiphilic dendrons have been shown to deliver chemotherapy drugs [35][36][37] and anti-cancer siRNAs [38][39][40] in tumors, thus efficiently suppressing tumor growth. Controllable assembly of complex supramolecular structures mimicking the cell surface [41], along with the possibility to decorate them with functional moieties, nanoparticles, or (bio)macromolecules [42] suggests that amphiphilic dendrons are highly emerging for designing precisely engineered biomaterials.

Most dendrimers currently in use for biomedical applications are composed of organic branches and generally mimic biopolymers: poly(amidoamine) dendrimers (PAMAM), poly(propylene imine) dendrimers (PPI), and poly(L-lysine) dendrimers (PLL) etc. [3][43][44][45][46][47][48][49][50][51][52][53]. Furthermore, there are dendrimers containing main

group heteroatoms as core components and branching points [5], such as silicon [54] or phosphorus [55], as well as their combinations with organic branches (PAMAM-organosilicon dendrimers (PAMAMOS)), phosphorus-viologen dendrimers [56], etc.

The major advantage of dendrimers and dendrons compared to other types of synthetic polymers is the precisely defined molecular structure [57], which facilitates their certification for use in drug formulations and medical devices. Furthermore, dendrimers and dendrimer-based nanoformulations are efficiently taken up by different cell types through clathrin-mediated endocytosis pathway [58]. In order to improve biocompatibility and biological activity, as well as achieve active targeting, dendrimers can be functionalized by various chemical and biological entities, such as polyethylene glycol, folate, signal peptides, ligands of cell surface receptors, etc. [57]. Reporter groups (fluorescent dyes, radioactive, or MRI-active groups) are introduced to monitor the biodistribution of dendrimer-based formulations. Rich dendrimer chemistry makes it possible to flexibly choose conjugation methods. The presence of multiple functional groups on the dendrimer surface gives room for obtaining multifunctional agents bearing different types of functional groups in a single construct. This helps decrease side effects of formulations [59].

Bioactive molecules can be either conjugated or complexed to dendrimers, and the complexation may involve hydrophobic or electrostatic interactions. In the case of nucleic acid therapeutics, they are usually bound by electrostatic interactions to dendrimers bearing cationic groups on the surface to form polyelectrolyte complexes [60].

2. The Use of Dendrimers for Biomedical Applications

Distinct dendrimer-based constructions have been subjected to clinical trials; their safety and efficacy have been demonstrated in Phases 1–3, although some studies are still ongoing. **Table 1** lists the dendrimer-based products involved in clinical trials, according to the clinicaltrials.gov database. These examples clearly highlight the growing employment of dendrimer-based drug delivery systems in the pharmaceutical industry.

Table 1. Dendrimer-based drugs in clinical trials.

Drug	Description of the Drug	Study Title	Study Dates	Brief Study Description	Company	Clinicaltrials.gov Identifier	Ref.
SPL-7013 Gel (VivaGel™)	G4 poly(L-lysine) dendrimer bearing 32 sodium 1-(carboxymethoxy) naphthalene 3,6-disulfonate on the surface	SPL7013 gel—male tolerance study	August 2006–June 2007	A phase 1, placebo-controlled study of the safety of a 3% *w/w* SPL7013 gel, administered to the penis of healthy male volunteers once	Starpharma Pty Ltd., Abbotsford, Australia	NCT00370357	[61]

Drug	Description of the Drug	Study Title	Study Dates	Brief Study Description	Company	Clinicaltrials.gov Identifier	Ref.
				daily for seven days			
SPL-7013 Gel (VivaGel™)	“	VivaGel™ in healthy young women	December 2006–November 2007	A phase 1, expanded, randomized placebo-controlled trial of the safety and tolerability of a 3% *w/w* SPL7013 gel in healthy young women when administered twice daily for 14 days	Starpharma Pty Ltd., Abbotsford, Australia	NCT00331032	[62]
SPL-7013 Gel (VivaGel™)	“	Safety and acceptability of SPL7013 gel (VivaGel™) in sexually active women	July 2007–December 2009	A phase 1 study of the safety and acceptability of a 3% *w/w* SPL7013 Gel applied vaginally in sexually active young women	Starpharma Pty Ltd., Abbotsford, Australia	NCT00442910	[63]
SPL-7013 Gel (VivaGel™)	“	Retention and duration of activity of SPL7013 (VivaGel®) after vaginal dosing	August 2008–March 2009	Phase 1 and phase 2 assessments of local retention and duration of activity following vaginal application of a 3% VivaGel in healthy volunteers	Starpharma Pty Ltd., Abbotsford, Australia	NCT00740584	[64]
SPL-7013 Gel (VivaGel™)	“	Dose-ranging study of SPL7013 gel for treatment of bacterial vaginosis (BV)	August 2010–May 2011	A phase 2, double-blind, multicenter, randomized, placebo-controlled, dose-ranging study to determine the efficacy and safety of the VivaGel administered vaginally in the	Starpharma Pty Ltd., Abbotsford, Australia	NCT01201057	[65]

Drug	Description of the Drug	Study Title	Study Dates	Brief Study Description	Company	Clinicaltrials.gov Identifier	Ref.
				treatment of bacterial vaginosis			
SPL-7013 Gel (VivaGel™)	“	Dose-ranging study of SPL7013 gel for the prevention of bacterial vaginosis (BV)	August 2011–December 2012	A phase 2, double-blind, multicenter, randomized, placebo-controlled, dose-ranging study to determine the efficacy and safety of the SPL7013 gel administered vaginally to prevent the recurrence of bacterial vaginosis	Starpharma Pty Ltd., Abbotsford, Australia	NCT01437722	[66]
SPL-7013 Gel (VivaGel™)	“	A phase 3 study of SPL7013 gel (VivaGel) for the treatment of bacterial vaginosis	April 2012–October 2012	A phase 3, double-blind, multicenter, randomized, placebo-controlled study to assess the efficacy and safety of a 1% SPL7013 gel for the treatment of bacterial vaginosis	Starpharma Pty Ltd., Abbotsford, Australia	NCT01577537	[67]
SPL-7013 Gel (VivaGel™)	“	A phase 3 study of SPL7013 gel (VivaGel) for the treatment of bacterial vaginosis	March 2012–July 2012	A phase 3, double-blind, multicenter, randomized, placebo-controlled study to assess the efficacy and safety of a 1% SPL7013 gel for the treatment of bacterial vaginosis	Starpharma Pty Ltd., Abbotsford, Australia	NCT01577238	[67]
SPL-7013 Gel	“	Efficacy and safety study of	October 2014–	A phase 3, double-blind,	Starpharma Pty Ltd.,	NCT02236156	[68]

Drug	Description of the Drug	Study Title	Study Dates	Brief Study Description	Company	Clinicaltrials.gov Identifier	Ref.
(VivaGel™)		SPL7013 gel to prevent the recurrence of bacterial vaginosis (BV)	October 2016	multicenter, randomized, placebo-controlled study to determine the efficacy and safety of the SPL7013 gel to prevent the recurrence of bacterial vaginosis	Abbotsford, Australia		
SPL-7013 Gel (VivaGel™)	“	Efficacy and safety study of SPL7013 gel to prevent the recurrence of bacterial vaginosis (BV)	October 2014–February 2017	A phase 3, double-blind, multicenter, randomized, placebo-controlled study to determine the efficacy and safety of the SPL7013 gel to prevent the recurrence of bacterial vaginosis	Starpharma Pty Ltd., Abbotsford, Australia	NCT02237950	[69]
AZD0466	Astra Zeneca cancer drug AZD4320, chemically conjugated to a PEGylated poly-lysine dendrimer	A Study of AZD0466 in patients with advanced hematologic or solid tumors	December 2019–June 2021	A phase 1, first-in-human study to determine the safety, tolerability, maximum tolerated dose (MTD), recommended Phase 2 dose (RP2D), and pharmacokinetics (PK) of AZD0466 in patients with solid tumors, lymphoma, and multiple myeloma at low, intermediate, or high risk for tumor lysis syndrome (TLS) with hematologic	Starpharma, Abbotsford, Australia; AstraZeneca, UK, Cambridge	NCT04214093	[70]

Drug	Description of the Drug	Study Title	Study Dates	Brief Study Description	Company	Clinicaltrials.gov Identifier	Ref.
				malignancies for whom no standard therapy exists			
AZD0466	“	A phase I/II study of AZD0466 as monotherapy or in combination with anticancer agents in advanced non-Hodgkin lymphoma	July 2022–November 2024 [Estimated]	A phase 1/2, modular, open-label, dose escalation and expansion, multicenter study of the safety, tolerability, PK, and preliminary efficacy of AZD0466 as a monotherapy, or in combination with other anticancer agents in patients with advanced NHL	Starpharma, Abbotsford, Australia; AstraZeneca, UK, Cambridge	NCT05205161	[71] [72]
AZD0466	“	Study of AZD0466 monotherapy or in combination in patients with advanced hematological malignancies	June 2021–June 2024 [Estimated]	A phase 1/2, modular, open-label, multicenter study to assess the safety, tolerability, pharmacokinetics, and preliminary efficacy of AZD0466 as a monotherapy and drug-drug interaction potential between AZD0466 and the azole antifungal voriconazole in participants with advanced hematological malignancies	Starpharma, Abbotsford, Australia; AstraZeneca, UK, Cambridge	NCT04865419	[73]
ImDendrim	G5 polylysine dendrimer mixed with nitro-imidazole-methyl-1,2,3-triazol-	Treatment of non-responding to conventional therapy inoperable liver	March 2017–December 2017	An open-label and unicenter study in patients with primary hepatocellular	National Institute of Allergy and Infectious Diseases	NCT03255343	[74]

Drug	Description of the Drug	Study Title	Study Dates	Brief Study Description	Company	Clinicaltrials.gov Identifier	Ref.
	methyl-di-(2-pycolyl) amine	cancers by in situ introduction of ImDendrim		cancer or metastatic liver cancer without standard therapeutic options for treatment, including chemotherapy or surgery	(NIAID), North Bethesda, Maryland, USA		
OP-101	G4 PAMAM dendrimer N-acetyl-cysteine	A study to evaluate the safety, tolerability, and pharmacokinetics of OP-101 after intravenous administration in healthy volunteers	March 2018–July 2018	A phase 1, open-label single ascending dose study to evaluate the safety, tolerability, and pharmacokinetics after intravenous administration in healthy volunteers	Orpheris, Inc. Redwood City, California, USA	NCT03500627	[75]
OP-101	“	A clinical study to measure the effect of OP-101 after being administered subcutaneous in healthy volunteers	March 2020–May 2020	A phase 1, open-label single ascending dose study to evaluate the safety, tolerability, and pharmacokinetics after subcutaneous administration in healthy volunteers	Orpheris, Inc. Redwood City, California, USA	NCT04321980	[76]
OP-101	“	A study to evaluate OP-101 (dendrimer N-acetyl-cysteine) in severe coronavirus disease 2019 (COVID-19) patients (PRANA)	August 2020–August 2022 [Estimated]	A phase 2, two-stage, double-blind, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics, and efficacy in patients with severe COVID-19	Ashvattha Therapeutics, Inc. Redwood City, California, USA	NCT04458298	[77]
D-4517.2	Hydroxyl dendrimer, VEGFR tyrosine kinase inhibitor	A study to evaluate the safety, tolerability, and pharmacokinetics	January 2022–August 2022	A phase 1, open-label, single-ascending dose study of the safety, tolerability,	Ashvattha Therapeutics, Inc. Redwood City,	NCT05105607	[78]

Drug	Description of the Drug	Study Title	Study Dates	Brief Study Description	Company	Clinicaltrials.gov Identifier	Ref.
		of D-4517.2 after subcutaneous administration in healthy participants		and pharmacokinetics after subcutaneous administration in healthy volunteers	California, USA		
D-4517.2	“	A study to evaluate the safety, tolerability, and pharmacokinetics of D-4517.2 after subcutaneous administration in subjects with neovascular (Wet) age-related macular degeneration (AMD), or subjects with diabetic macular edema (DME) (Tejas)	August 2022–June 2023 [Estimated]	A phase 2, two-stage study: open-label assessment of safety and pharmacodynamic response as well as a visual examiner-masked, randomized active, sham, and placebo controlled study evaluating the efficacy of D-4517.2 administered subcutaneously to subjects with neovascular age-related macular degeneration or subjects with diabetic macular edema	Ashvattha Therapeutics, Inc. Redwood City, California, USA	NCT05387837	[79]
siCoV/KK46	Anti-SARS-CoV-2 siRNA (targeting RNA-dependent RNA polymerase)/KK-46 (peptide dendrimer) complex	The siCoV/KK46 drug open-safety study	January 2021–March 2021	A phase 1, open-label, dose-escalation study to assess the safety and tolerability of single and multiple doses in healthy volunteers (inhalation use)	National Research Center — Institute of Immunology FMBA, Saint Petersburg, Russia	NCT05208996	[80]
MIR 19®	“	Evaluation of safety and efficacy of a MIR 19 ® inhalation solution in patients with	April 2021–September 2021	A phase 2, multicenter controlled randomized study to assess the efficacy and	National Research Center— Institute of Immunology FMBA, Saint	NCT05184127	[81]

Drug	Description of the Drug	Study Title	Study Dates	Brief Study Description	Company	Clinicaltrials.gov Identifier	Ref.
		moderate COVID-19		safety of MIR 19® via 14 days of treatment of participants with symptomatic moderate COVID-19	Petersburg, Russia		

The first dendrimer-based, anti-microbial drug approved for use in humans was Vivagel® (SPL7013) (Starpharma, Abbotsford, Australia), a poly-L-lysine dendrimer derivastive used as a topical microbicide for the prevention and treatment of bacterial vaginosis (BV). There have been at least 13 clinical studies of this product, with the first clinical trial completed in 2004. SPL7013 is a polyanionic dendrimer with a benzylhydramine lysine core and has 32 naphthalene disulfonate surface functionalities (**Figure 2**). This product also provides the prevention of genital herpes (HSV-2), HIV, and other sexually transmitted infections (STIs). Studies have shown that SPL7013 is generally well tolerated with minimal side effects [82][83][84][85][86][87][88][89][90][91]. SPL7013, in the form of a nasal spray called VIRALEZE, has also undergone a first growth phase as registered in the Australian and New Zealand Clinical Trials Registry [92].

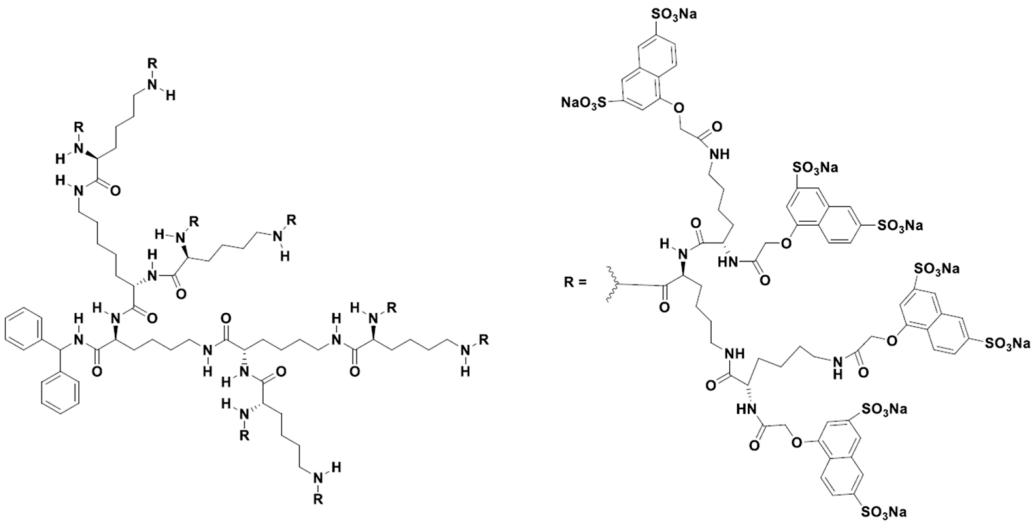

Figure 2. Two-dimensional chemical structure of VivaGel® [92].

Another example of a poly-L-lysine dendrimer developed by Starpharma and AstraZeneca is AZD0466. This is a fifth generation poly-L-lysine dendrimer, a highly optimized molecule containing the anti-cancer drug AZD4320, and a PEGylated poly-L-lysine dendrimer. AZD0466 belongs to a new class of oncology drugs that provide efficient delivery of a dual Bcl-2/xL inhibitor with an optimized release profile that is designed to reduce the potential for toxicity associated with dual Bcl-2/xL inhibition [93][94][95][96]. The AZD0466 construct is currently undergoing simultaneous phase1/phase 2 clinical trials in patients with advanced hematologic malignancies as monotherapy or in combination with certain combination therapies, such as antifungals.

Another example is a fifth-generation poly-L-lysine-based dendrimer named ImDendrim, which has proven to be suitable for encapsulating rhenium and radioactive 188Re. This potential radiopharmaceutical agent showed antitumor activity in liver cancer in mice [97]. The clinical study of this drug concerns patients with an inoperable liver tumor that is resistant to other classical chemotherapy.

PAMAM dendrimers [44][98][99][100][101][102][103] are the most widely used dendrimers. In their native form, they can be easily modified as desired. However, low storage stability has long precluded the use of PAMAM dendrimers in clinical trials [104]. However, PAMAM dendrimers have recently passed clinical trials proposed by Ashvattha Therapeutics.

The first PAMAM dendrimer-based injectable is OP-101, a covalent conjugate of generation 4 hydroxyl-terminated poly(amidoamine) dendrimer and N-acetylcysteine (NAC) developed by the American firm Ashvattha Therapeutics and its subsidiary Orpheris, Inc. Safety trials for intravenous and subcutaneous injections in healthy volunteers began in 2018 and continued into 2020. The study is not yet complete, but preliminary results indicate that OP-101 is well tolerated and may have the potential to treat systemic inflammation and neuronal damage, reducing the disease severity and mortality in patients [105].

Another drug from the same company, Ashvattha Therapeutics, with the open name D-4517.2, is a hydroxyl dendrimer, a VEGFR tyrosine kinase inhibitor. Initial studies have shown that this drug is safe and well tolerated, with only a few patients experiencing mild transient reactions at the injection site associated with the technique [106].

Two clinical trials against COVID-19 were conducted in 2021, both based on the same cationic peptide dendritic structure containing lysine as branch elements, named KK-46, the structure of which is shown in **Figure 3**.

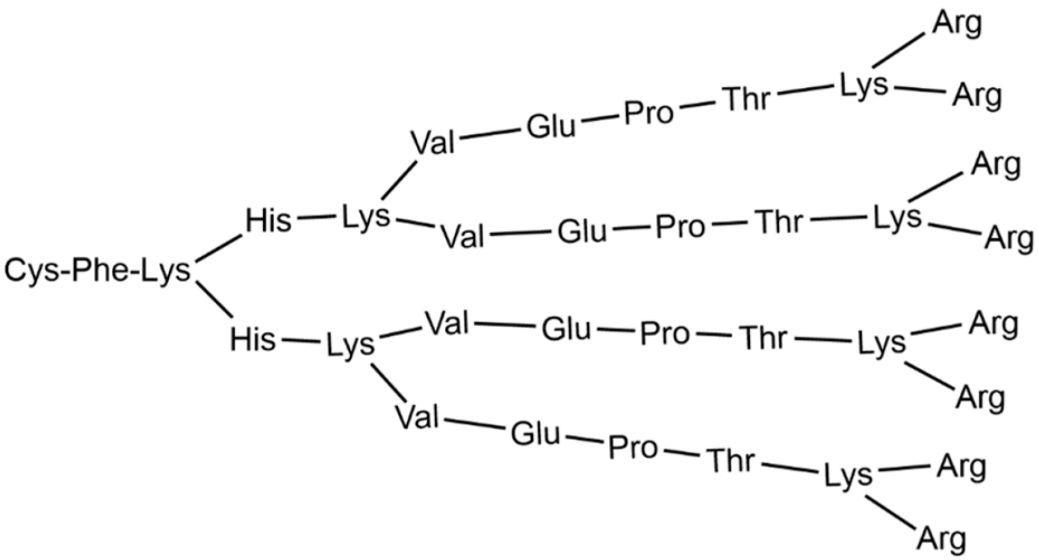

Figure 3. Structure of the cationic peptide dendrimer KK-46, usable as carrier of siCoV [107].

This compound, developed by the Institute of Immunology of the Federal Medical and Biological Agency of Russia, in collaboration with the St. Petersburg Research Institute of Vaccines and Serums, is used as a carrier of siRNA, modified to suppress SARS-CoV-2 (siCoV) by inhibiting its replication [108]. The association of KK-46 with siCoV has been named MIR 19® [109]. Based on preclinical data, the researchers hypothesized that SARS-CoV-2 inhibition by siCoV/KK46 could potentially reduce lung inflammation, thereby improving treatment outcomes. According to the test results, the drug was registered and introduced into civil circulation by the Ministry of Health of the Russian Federation on 22 December 2021 LP-007720 as a direct-acting antiviral agent [110].

3. Conclusion

In summary, distinct dendrimer-based constructs have been clinically tested and have been shown to be safe and effective in Phases 1–3, with some studies still ongoing. Table 1 lists dendrimer-based products in clinical trials, according to the Clinictrials.gov database. These examples clearly highlight the growing use of dendrimer-based drug delivery systems in the pharmaceutical industry.

Thus, dendrimers represent a useful platform for the development of safe vaccines with new properties and application potential and will also be useful for basic research on the mechanisms underlying the induction and control of immunity.

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