



HAL
open science

First-in-class and best-in-class dendrimer nanoplatfroms from concept to clinic: Lessons learned moving forward

Serge Mignani, Xangyang Shi, João Rodrigues, Helena Tomas, Andrii Karpus, Jean-Pierre Majoral

► To cite this version:

Serge Mignani, Xangyang Shi, João Rodrigues, Helena Tomas, Andrii Karpus, et al.. First-in-class and best-in-class dendrimer nanoplatfroms from concept to clinic: Lessons learned moving forward. *European Journal of Medicinal Chemistry*, 2021, 219, pp.113456. 10.1016/j.ejmech.2021.113456 . hal-03275575

HAL Id: hal-03275575

<https://hal.science/hal-03275575v1>

Submitted on 24 Apr 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

First-in-class and Best-in-class Dendrimer Nanoplatfroms From Concept to Clinic: Lessons Learned Moving Forward

Serge Mignani^{*a,b}, Xangyang Shi^{*c,b}, João Rodrigues^{*b}, Helena Tomas,^b
Andrii Karpus^{d,e}, and Jean-Pierre Majoral^{*d,e}

^a Université Paris Descartes, PRES Sorbonne Paris Cité, CNRS UMR 860, Laboratoire de Chimie et de Biochimie Pharmacologiques et Toxicologique, 45, rue des Saints Peres, 75006 Paris, France

^b CQM - Centro de Química da Madeira, MMRG, Universidade da Madeira, Campus da Penteadá, 9020-105 Funchal, Portugal

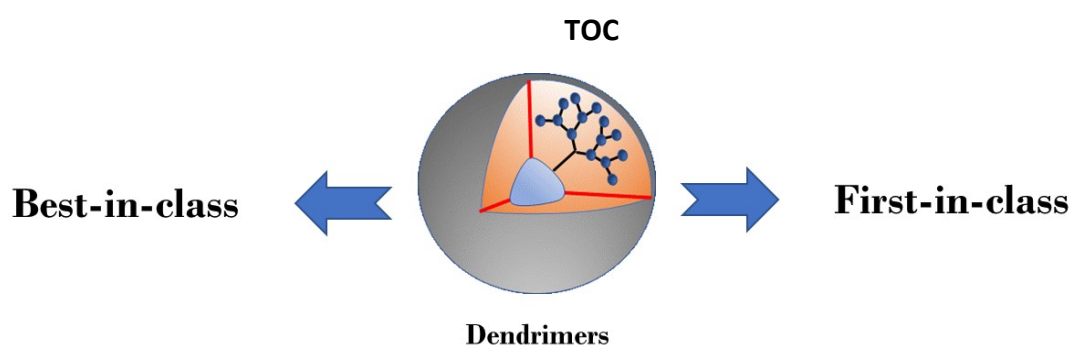
^c College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, Shanghai 201620, PR China

^d Laboratoire de Chimie de Coordination du CNRS, 205 route de Narbonne, 31077, Toulouse Cedex 4, France

^e Université Toulouse 118 route de Narbonne, 31077 Toulouse Cedex 4, France

Corresponding authors

S. Mignani: serge.mignani@parisdescartes.fr, serge.mignani@staff.uma.pt; **X. Shi:** xshi@dhu.edu.cn; **J-P. Majoral:** majoral@lcc-toulouse.fr; **J. Rodrigues:** joaor@uma.pt



Highlights

- First-in-class and best-in-class dendrimers profile analyse
- Marketed and clinical dendrimers in nanomedicine analyse
- Lessons learned moving of dendrimers from concept to clinic

Contents :

1. Introduction
2. First-in-class *versus* best-in-class approaches in drug discovery strategy: Concise general aspects
3. *In vivo* biocompatibility of nanomedicine: a concise overview

4. Why are dendrimers of interest to develop in the nanomedicine domain?
 - 4.1. General aspects of dendrimers at a glance
 - 4.2. Possibilities of modifying dendrimer architectures for use in nanomedicine
 - 4.3. Pharmacokinetics and biodistribution of dendrimers in the oncology realm: general aspects
 - 4.4. Near-infinite possibilities for the use of dendrimers for delivery of drug products *in vitro* and *in vivo* based on best-in-class drug development strategy for known drugs
 - 4.5. Near-infinite possibilities, but few examples, for the use of dendrimers as drugs themselves based on first-in-class drug development strategy
5. Marketed and clinical dendrimers in nanomedicine
 - 5.1. Dendrimers in the clinical realm: very few examples to date!
 - 5.2. What are the biggest challenges in dendrimer development for dendrimer translation into the clinic?
6. Conclusion and prospects
7. References

ABSTRACT

Research to develop active dendrimers by themselves or as nanocarriers represents a promising approach to discover new biologically active entities that can be used to tackle unmet medical needs including difficult diseases. These developments are possible due to the exceptional physicochemical properties of dendrimers, including their biocompatibility, as well as their therapeutic activity as nanocarriers and drugs themselves. Despite a large number of academic studies, very few dendrimers have crossed the 'valley of death' between. Only a few number of pharmaceutical companies have succeeded in this way. In fact, only Starpharma (Australia) and Orpheris, Inc. (USA), an Ashvattha Therapeutics subsidiary, can fill all the clinic requirements to have in the market dendrimers based drugs/nanocarriers. After evaluating the main physicochemical properties related to the respective biological activity of dendrimers classified as first-in-class or best-in-class in nanomedicine, this original review analyzes the advantages and disadvantages of these two strategies as well the concerns to step in clinical phases. Various solutions are proposed to advance the use of dendrimers in human health.

1. Introduction

From a cursory glance, over the last decade, nanomedicine uses various powerful nanotechnologies and specific nano-objects to develop innovative applications in the health

field, by exploiting the intrinsic physical, chemical and biological properties of these versatile nanoscale materials.[1,2] With this transversal character of nanomedicine, one enters into the world of the infinitely small, with a scale of less than 200 nanometers. Therefore, the idea is to act on the same scale as human tissues, molecules, cells, DNA (microRNA and SiRNA), proteins, viruses, and bacteria. The main goal is the development of new medical techniques for diagnosis, therapy and patient monitoring. Thereby, the use of nonviral nanovectors capable of transporting and then releasing the active drug into the specific target cells, encompassing cancer or inflammatory pathologies and nano-objects, capable of amplifying the effect of radiotherapy by preserving healthy tissue and improving diagnosis.[3] Within the huge chemical space, approved nanoformulations, including PEGylated and non-PEGylated liposomes, nanocrystals, nanoparticles (NPs) and dendrimers, have been realized for the application of nanotechnology in medicine. The other NPs used in nanomedicine are polymer-drug conjugates, polymer-protein conjugates, polyplexes, micelles and degradable nanogels.[4]

This review seeks to summarize and analyze challenges and limitations during active research development, including clinical translation factors, as well as to challenge current dogmas of carefully-assembled dendrimers as first-in-class and best-in-class NPs. Potential solutions to improve the rate of success are, in the end, proposed.

2. First-in-class versus best-in-class approaches in drug discovery strategy: Concise general aspects

Any pharmaceutical organization is broken down into two classes of program strategy: first-in-class[5] and best-in-class. The choice is not trivial, due to limited resources and the balance between risks and benefits.[6,7] The first-in-class program is based on new science (*e.g.*, mechanism of action), with the aim to produce the first types of molecular entities and new therapies, giving unprecedented patient outcomes with superiority over existing treatments. However, novelty does not necessarily lead to success! An interesting analysis by Eder *et al.* showed that phenotypic screening strategies have been more productive than target-based approaches in the discovery of first-in-class small-molecule drugs.[8] Another interesting analysis was performed by Schulze and Ringel regarding the value of first-in-class versus best-in-class. First-in-class is slightly better than best-in-class (2nd), and much better than best-in-class (3rd).[9] In the best-in-class program, there are competitor(s), who are already in the clinic or on the market, showing efficacy in patients. The proposed drug must possess an improvement over its competitor(s). The advantage of the best-in-class strategy is to be able to use studies from competitors for information alongside the clinical trials. As highlighted by Swinney,[10] the distribution of new drugs (NMEs) found between 1999 and 2008 is as follows: the most successful first-in-class drugs were found using phenotypic screening and then target-based screening, whereas the follower drugs come from target-based screening with a successful rate strongly higher than phenotypic screening. Consequently, we can flip-flop these strategies of development in the field of nanomedicine. Thus, a nanoparticle encapsulating or conjugating a biologically active molecule that is used clinically (as drug) can be considered to be best-in-class because it improves the

physicochemical properties as well as the biological activity of the considered drug, while a new nanoparticle (NP) that is active by itself is considered to be first-in-class.

3. *In vivo* biocompatibility of nanomedicine: a concise overview

Nano-drugs improve the benefit/risk ratio of drugs by increasing their efficacy and bioavailability in the target tissue or organ while reducing administered doses and toxicity risk. For instance, conventional drugs, recombinant proteins, vaccines, aptamers, siRNA, nucleotides and genes have been carried by NPs.[11,12] Targeted[13] and non-targeted approaches have been developed. These have improved the benefit/risk ratio of encapsulated/conjugated or complexed drugs, by increasing their efficacy and bioavailability in the target tissue or organ, while reducing the doses to be administered and the risk of toxicity. To this end, as shown in Figure 1, an outstanding analysis of the *in vivo* biocompatibility of NPs has been performed by Khandare and Haag *et al.*[14]

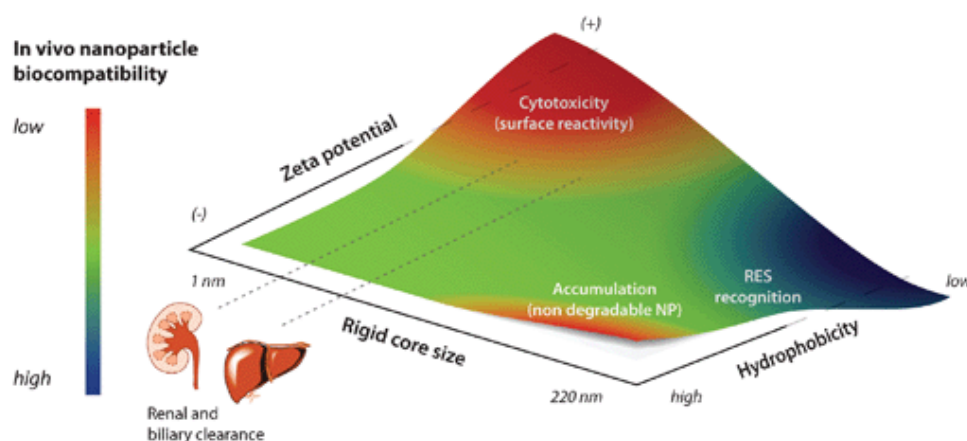


Figure 1. Parameters determining *in vivo* biocompatibility in nanomedicine. Reproduced with permission from ref. 14, The Royal Society of Chemistry.

Designed versatile lipid-based NPs, liposomes and natural (*e.g.*, chitosan, collagen) and synthetic (*e.g.* poly(lactide-co-glycolide) (PLGA)) polymeric NPs[15], dendrimers and quantum dots are the main types of NPs used in nanomedicine, for a variety of biomedical uses.[16,17] In the clinic, as best-in-class NPs, different formulations of polymer micelles, emulsions and solid particles have been used to incorporate drugs.[18] As examples, Caelyx[®], Doxil[®], Transdrug[®] [19] and Abraxane[®] (ABI-007) are currently on the market for tackling cancer, including metastatic breast and pancreatic cancer, advanced melanoma (Abraxane), and to treat one form of hereditary amyloidosis (Onpattro[®]).[20] Caelyx[®] and Doxil[®] are PEGylated liposomes for iv administration, as is encapsulated hydrophobic doxorubicin (DOX, Adriamycin).[21] PEGylated liposomal doxorubicin (Caelyx[®]), administered alone or in combination with tamoxifen, is safe and moderately effective in patients with recurrent high-grade III glioma.[22] Doxil[®] was the first NP approved by the FDA in 1995, and, recently, a generic version named Lipodox[®] started to be produced by Sun Pharmaceutical Industries Ltd in India. Other liposomal formulations of DOX are D-99,

Myocet[®], the thermosensitive liposome ThermoDox[®], and polymeric NPs (Livatag[®]), whereas the liposomal form of daunorubicin is named DaunoXome[®]. The second NP of high interest is Abraxane[®], developed by Abraxis BioScience and AstraZeneca.[23] This NP represents the first albumin-bound drug commercially available to treat tumors, formed by the complexation of Taxol with albumin, and shows an original cremophore-free NP.

4. Why are dendrimers of interest to develop in the nanomedicine domain?

4.1. General aspects of dendrimers at a glance

From a cursory glance, the dendrite structure is a very common pattern in nature; above ground, trees use dendritic growth to improve the exposure of their leaves to sunlight. This process, known as photosynthesis, is crucial for trees to maintain life and growth. In the field of organic synthesis, the design of dendritic molecules is a relatively new field; for instance, in drug delivery, pioneered in 1978 by Vögtle and colleagues.[24] Then, Tomalia *et al.* named this new class of versatile NPs "dendrimers", formed from the two Greek words "dendros", meaning "tree" or "branch", and "meros", meaning "part".[25] As shown in Figure 2, well-defined synthetic polymers (dendrimers) have a well-defined structure, compared to the hyperbranched polymers of which they are a subset.

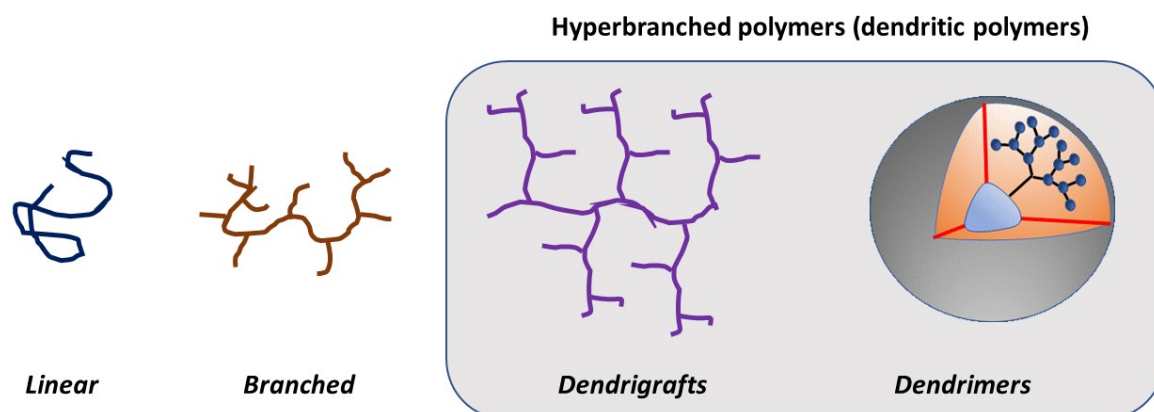


Figure 2. General 2D chemical representation of linear, branched and hyperbranched polymers including dendrimers.

Dendrimers have a symmetric repetition of branches (termed generation) starting from a core, having a three-dimensional morphology of nanometer-scale size and precise molecular weight. Dendrimers can be classified thus far by their generation number (G0, G1, G2, G3, and G4, etc.) and have a 'spherical' shape (Figure 3). The central core as a focal point, branches and multiple terminal groups, which increase exponentially with each generation, are the main construction elements of the dendrimers, acting as a scaffolding from its base to its top. Both the engineered nature of the dendrimer surface and its surface density are crucial and dictate its biological interactions with living systems in terms of biological activity and physicochemical properties.[26,27,28] The release of drugs into the cells by positively-charged dendrimers is achieved by the interactions of these dendrimers with negatively-charged biological and cell membranes, for penetration purposes.[29]

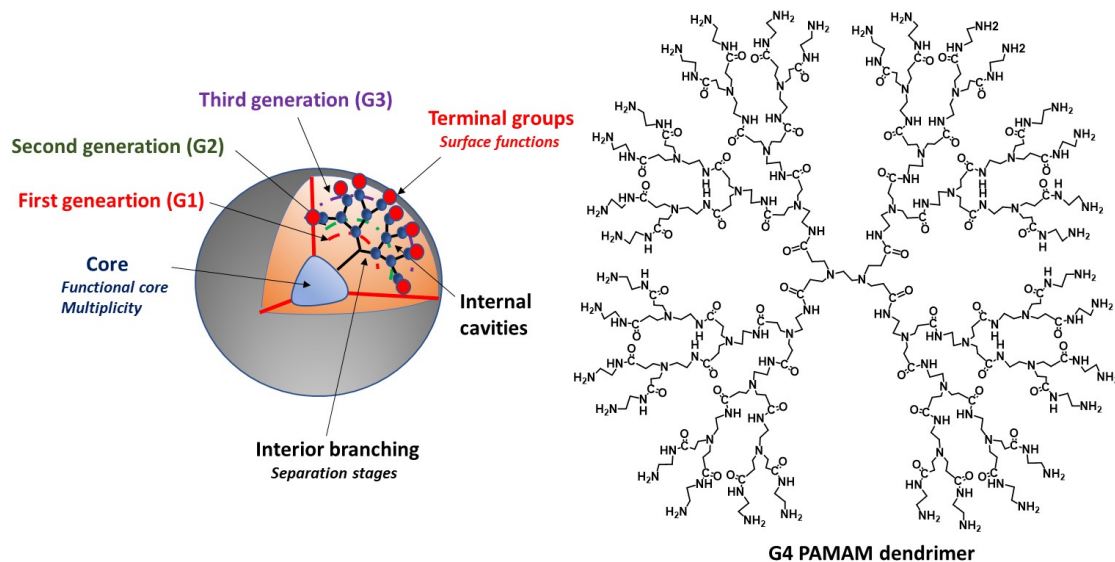


Figure 3. 2D general representation of dendrimers including core, internal cavities, interior branching and generations, and G4 PAMAM dendrimer as an example of dendrimer.

The number of articles about describing dendrimers in the Scopus database by year is shown in Figure 4.

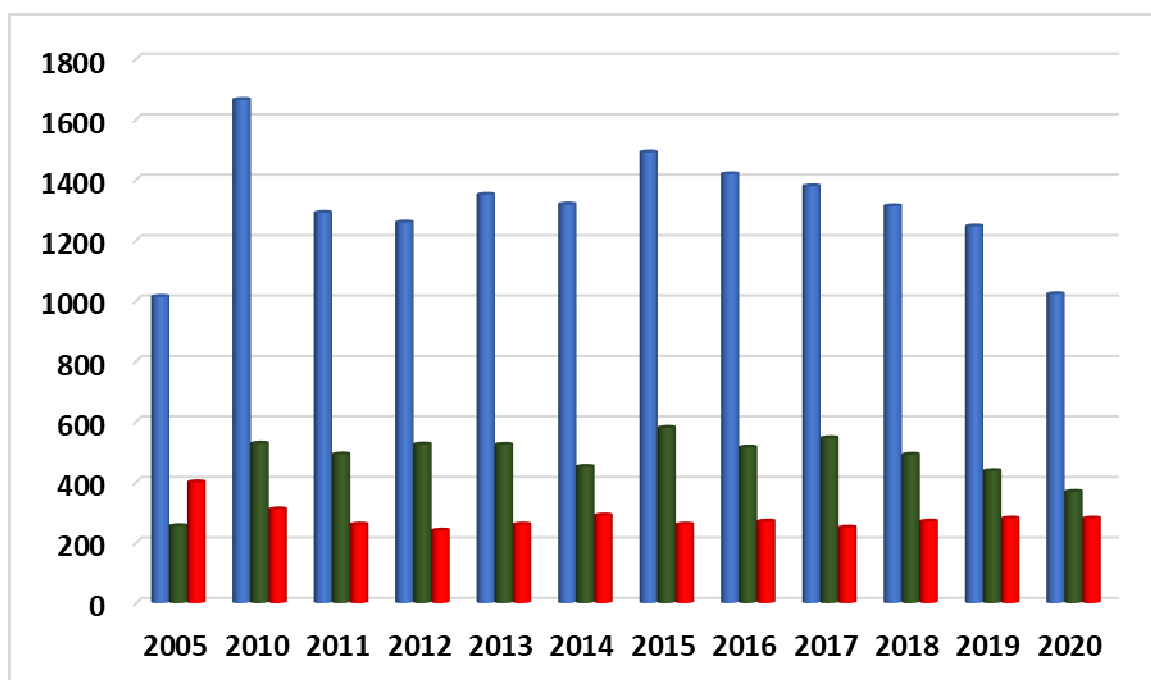


Figure 4. Number of articles about dendrimers in Scopus database (blue bars: all fields; green bars : biomedical field (biochemistry, genetics, molecular biology, pharmacology, toxicology and pharmaceutics ; red bars : ratio (all fields/biomedical field)x100)

Tunable dendrimers can be synthesized by step-wise chemical synthesis approaches, by both divergent and convergent[30] methods. Nevertheless, step-wise synthesis limits their ease of preparation for large generations (above generation 3), despite the fact that single-step

methods from AB2 or AB5 monomers have been developed.[31] Recently, a highly interesting approach has been demonstrated by Lu *et al.*, which consists of using a monomer with hierarchical reactivity.[32] To date, there are over 100 families of dendrimers consisting of a panoply of atoms, including C, H, S, P, O, Si and metals, such as Au.[33] The most commonly used type of dendrimers families are the poly(amidoamine) (PAMAM)[25] and poly(propyleneimine) (PPI)[24] dendrimers, as they are commercialized. Other types of dendrimers include phosphorous,[34] carbosilane,[35] poly(L-lysine) (PLL),[36] poly(esteramide),[37] peptide[38] polyurea and bioinspired tryptophan-rich peptide (TRPD) dendrimers.[39] Multiple routes of administration can be used.[40]

4.2 Possibilities of modifying dendrimer architectures for use in nanomedicine

Interestingly, based on quantized hard and soft nanoscale building blocks (having defined size, shape, surface chemistry, flexibility/rigidity, elemental composition and architecture), the concept of a nano-periodic road map has been highlighted by Tomalia and colleagues.[41] As a general trend, higher-generation cationic dendrimers have shown cytotoxicity and hemolysis effects,[42] whereas anionic dendrimers, including sulfonated, carboxylated and phosphonated dendrimers, and neutral dendrimers, bearing poly(ethylene oxide), PEG chains and acetyl, carboxyl, mannose and galactose end groups, exhibited less toxicity vs. positively-charged dendrimers. The two main challenges for the use of dendrimers in nanomedicine are achieving low polydispersity and biocompatibility.[43] In agreement with Frechet and Szoka *et al.*, the success of dendrimers in nanomedicine as nanocarriers and as drugs (active *per se*) depends largely on their biocompatibility.[44] An interesting analysis was performed by Ciolkowski and colleagues regarding the cytotoxicity of PAMAM dendrimers, relating cytotoxicity to physical properties such as surface polarity.[45] Several reviews highlight the *in vitro* and *in vivo* biocompatibility profiles of dendrimers, represented in Figure 5.[26,27, 46]

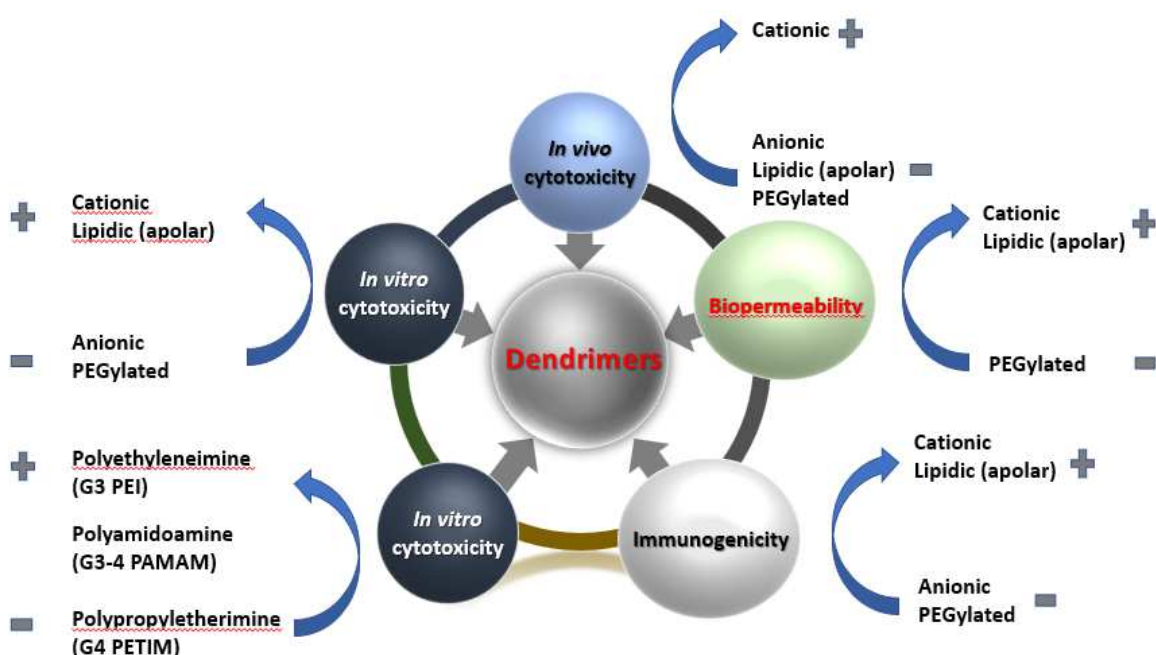


Figure 5. Schematic depiction of *In vitro* and *in vivo* biocompatibility profiles of dendrimers.

4.3. Pharmacokinetics and biodistribution of dendrimers in the oncology realm: general aspects

During the development of drugs, in general, and of NPs, particularly dendrimers, the control of their pharmacokinetics and biodistribution plays an important role in their *in vivo* therapeutic applications, as well as in their clinical translation. To this end, in a tutorial review, Frechet, Szoka and colleagues studied the role of molecular weight and architecture on the *in vivo* behavior of dendrimers in oncology.[44] Chemical control of the dendrimer architecture influences two very important parameters, which are: the high drug elimination half-life, linked to the long blood circulation half-life, which is the major requirement for the enhanced permeation-and-retention (EPR) effect; and the appropriate rate of release of the drug within the cancer cell target. Indeed, a too-rapid release of drugs from dendrimers may result in a loss of the drug before it enters the tumor, and, ergo, not enough drug concentration in the tumor to induce the desired antiproliferative effect. As shown in Figure 6, four kinetic parameters were introduced in a model depicted by the authors: rate-controllable elimination constant ($K_{\text{elimination}}$), which is a function of renal, liver and splenic clearance, related to the physicochemical properties of the dendrimers, $K_{\text{extravasation}}$ which depends on tumor characteristics such as size, vascular permeability and convective flow, as well as on physicochemical properties of dendrimers, including size, shape and surface characteristics.[47] The first order release parameter, K_{release} depends on the nature of the linker between the drugs and the dendrimers (conjugation approach), or on the nature of the dendrimers (encapsulation and complexation approaches). The K_{washout} parameter is a function of the drug characteristics, and is related to the rate of the half-life drug elimination.

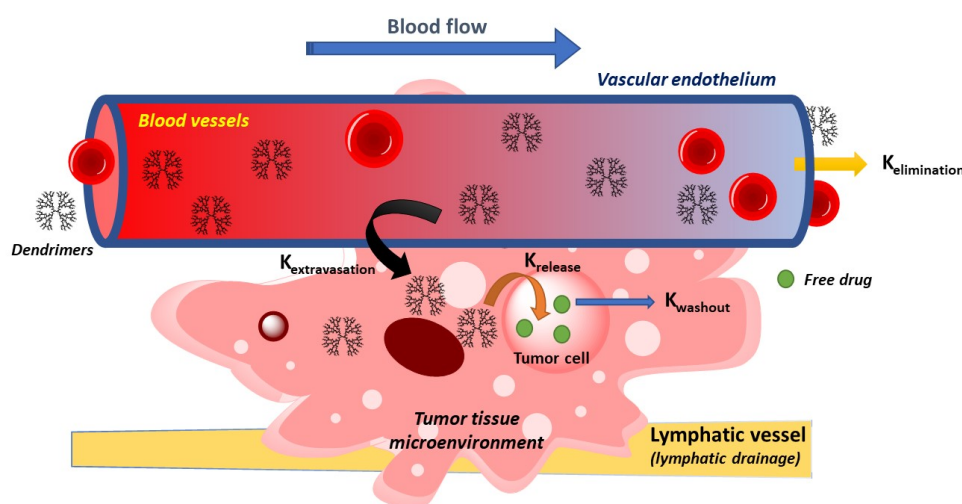


Figure 6. Representation of Kinetic parameters for the drug penetration in tumors: $K_{\text{elimination}}$, $K_{\text{extravasation}}$, K_{release} and K_{washout} .

Frechet, Szoka et al. proposed a simple mathematical model, using pharmacokinetic data, of the concentration of free drug *versus* time after iv injection, related to the half-life of the drug release. [44] A decrease of the half-life drug elimination (rapid release rate, 1 h)

induced the release of the drug prior to entering the tumor. Between 10 and 50 h, peaks in release were observed, whereas for a higher half-life of drug release (500 h), very low release was observed. As indicated by the authors, the selection of most appropriate linker by chemists is crucial to control the concentration of the free drug in the tumor, and the chemistry also has a high impact in the evaluation of K_{release} and K_{washout} parameters.

An additional important analysis was performed by Wijagkanalan *et al.*, regarding the relationship between physicochemical properties (M_w and charge) and pharmacokinetic parameters (area under the curve [AUC], hepatic [hepatic plasma flow rate] and renal [glomerular filtration rate] clearance) of proteins and dendrimers, following iv administration in mice (Figure 7).[48] This study is in full agreement with those of Haag *et al.* (*vide supra*) regarding the biocompatibility of NPs.[14] The lysine dendrimers (generation 4–6) were mainly eliminated through renal clearance, for PAMAM dendrimers higher than G6. The amphiphilic PEGylated G6 lysine and PAMAM dendrimers were eliminated through hepatic clearance, and, importantly, demonstrated a higher AUC than the corresponding non-PEGylated dendrimers. These PEGylated dendrimers escape uptake by the non-specific reticuloendothelial system (RES). The bovine immunoglobulin (IgG) and bovine serum albumin (BSA) were eliminated through hepatic clearance, and showed a higher AUC than the PEGylated G6 PAMAM dendrimer. Anionic and cationic BSA (Su-BSA and Cat-BSA) were cleared mainly *via* the hepatic pathway. Cationic and anionic superoxide dismutases SOD (Cat-SOD and Suc-SOD) were eliminated through both renal and hepatic clearance, whereas SOD was eliminated mainly *via* renal clearance. Interestingly, the therapeutic availability (TA), which is the ratio of total drug amount or drug activity of dendrimer–drug to free drug in the target tissue, was 1–38, 0.7–3 and >300 (few cases analyzed) for drugs conjugated, encapsulated and complexed with dendrimers, respectively. An important survey was published relating dendrimer pharmacokinetics profiles to the absorption, distribution, metabolism and elimination (ADME) properties of dendrimers, including size, structure and surface functionality.[49]

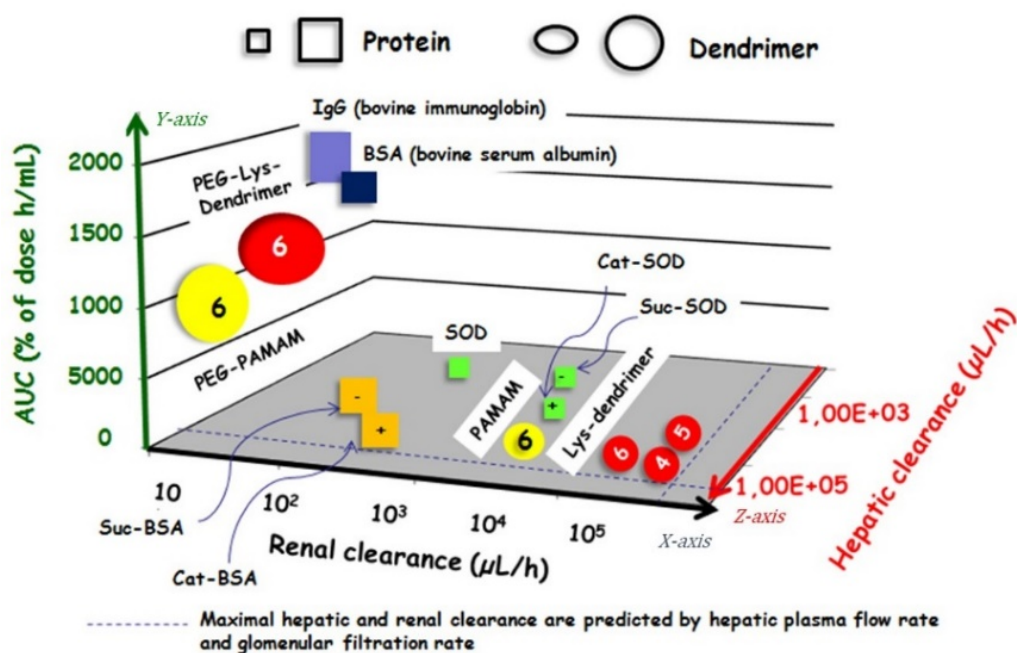


Figure 7. Pharmacokinetic parameter (AUC, renal and hepatic clearance) related to dendrimer characteristics. Adapted from ref. 48

As highlighted by Cheng and colleagues, conjugation of drugs allowed better control over drug release than did encapsulation and electrostatic complexation of drugs, using dendrimers as nanocarriers based on best-in-class strategy.[50]

4.4. Near-infinite possibilities for the use of dendrimers for delivery of drug products in vitro and in vivo based on best-in-class drug development strategy for known drugs

For biomedical applications, the valorization of dendrimers has been demonstrated by their useful nano-carrier developments, using their host-guest properties, a concept introduced by Maciejewski in 1982,[51] for the delivery of targeted drugs[52,53,54, 55] and genes[56] (in the majority of studies); however, importantly, several studies have shown that some have their own therapeutic properties for specific medicinal uses, although few of such studies are reported to date.[57]

Numerous publications and reviews present the use of dendrimers as nano-carriers *via* encapsulation (drug loading) and electrostatic complexation, which preserves the chemical integrity and pharmacological properties of the drugs, or conjugation, such as with anti-cancer agents for targeted and non-targeted antineoplastic therapy (*e.g.*, cisplatin, paclitaxel, 5-fluorouracil, camptothecin [CPT], methotrexate, doxorubicin),[46,58] as well natural products, [46,59,60] antisenses,[61], aptamers,[62] and siRNAs.[63] Figure 8 depicts several dendrimer types used in therapeutic domains with conjugated or complexed (siRNAs) drugs. The other therapeutic realms for drug delivery using dendrimers are: 1) anti-inflammatory therapy, by delivery of non-steroidal anti-inflammatory drugs (NSAIDs) which include ibuprofen;[64] 2) antibacterial therapy, against Gram positive and Gram negative bacterial strains and parasites (*e.g.*, Leishmania), by delivery of several types of drugs (*e.g.*, nadifloxacin, prulifloxacin, erythromycin, azythromycin, vancomycin, amoxicillin, ceftazidime, amphotericin B, tobramycin, and fusidic acid);[46,65] 3) antiviral therapy, by delivery of both small compounds (*e.g.*, zidovudine, efarvenz, mariviroc, tenofovir, oseltamivir, and acyclovir) and siRNAs (glycoprotein H, heparin sulfate);[66] 4) cardiovascular therapy, by delivery of siRNAs and a ramipril-hydrochlorothiazide mixture.[67]

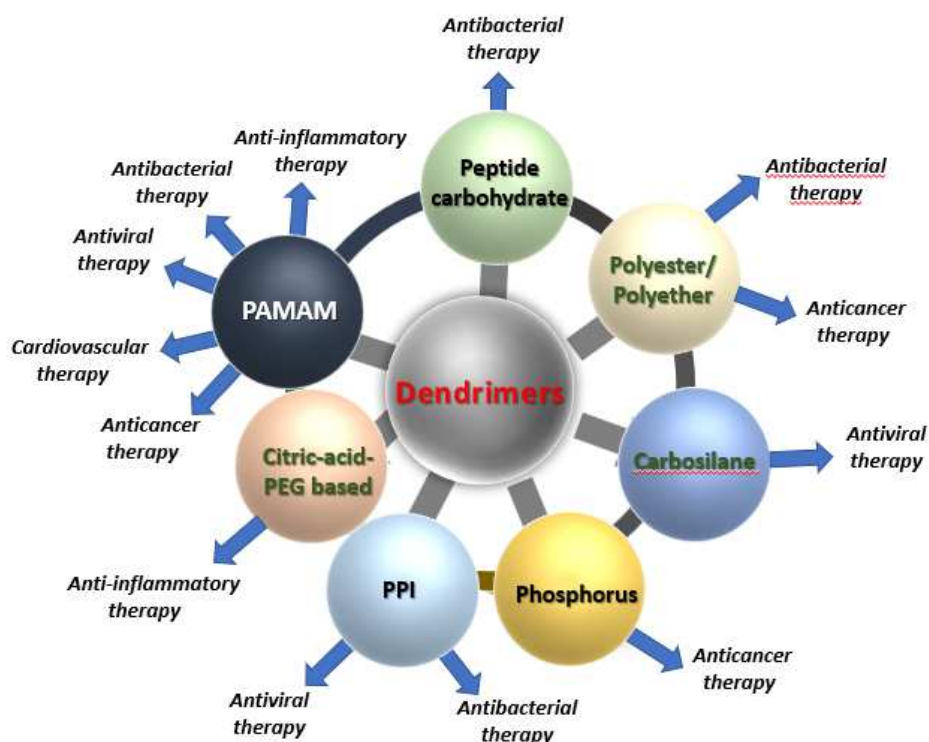


Figure 8. Dendrimers used in therapeutic domains with conjugated or complexed (siRNAs) drugs. See text for references

In an unusual and interesting study regarding the development of dendrimers for the release of DOX (best-in-class drug development strategy), Fréchet *et al.* pointed out that the PK/PD profile of the asymmetrical G1–G3 bow-tie dendrimers was related to their molecular weight and to architectural effects (length of the PEG chains). Several pharmacological properties can be outlined: 1) no significant cytotoxicity; 2) significant *in vitro* biodegradability (hydrolysis reaction); 3) strong chemical stability in buffer solutions at both mildly acidic pH (5.0) and a normal physiological pH (7.4) at 37 °C; 4) for generation 3 dendrimers, long circulation times with high elimination half-lives of 31–50 h (mice, iv administration); 5) an increase in generation (G2 over G3) decreased the renal clearance, and polymers of generation 3 were excreted more slowly into the urine *versus* generation 2 polymers. Interestingly, *iv* administration in mice with B16F10 melanoma of 40 mg/kg of G3 bow-tie dendrimers showed similar biodistribution behaviors, regardless of the length of the PEG chains. The highest concentrations of polymers in both the tumor and blood were observed at 48 h. Cheng *et al.* [68] highlighted the influence of the nature of the linker between the conjugated drug and the surface of dendrimers on the PK/PD profile of the delivery of the drug using PEGylated poly(L-lysine) dendrimer-CPT conjugates. Two different linkers between the lysine dendrimer and CPT were used: glycine linker and b-alanine linker. Interestingly, the glycine linker displayed a half-life approximately 10-fold lower than the b-alanine linker. This type of construction showed *in vivo* improvements in mice *vs.* CPT alone, as follows: 1) improvement of the solubility of CPT; 2) increase in the circulation half-life of CPT, inducing an increase in its blood circulation time; 3) strong enhancement in tumor uptake (approximately 10-fold over CPT alone); 4) improvement of antitumor efficacy in

subcutaneous (sc) C26 murine and HT-29 human colon carcinoma tumor models vs. CPT alone. Remarkably, a single injection of PEGylated poly(L-lysine) dendrimer-CPT conjugate into C26-tumored mice significantly prolonged survival and delayed tumor growth, compared to the control group or to treatment with CPT alone.

These studies clearly demonstrate the usefulness of dendrimers that conjugate or encapsulate drugs in the treatment of cancers, for example, by improving their intrinsic biological activity. The use of these NPs, as pointed out by other authors, is a potentially significant advance in the treatment of cancer by drugs such as Doxil® and Abraxane® (*vide supra*). Therefore, this strategy, makes it possible to improve the overall efficacy of these drugs, and for NPs such as dendrimers to eventually become known as 'best-in-class' compounds.

The optimization of dendrimer architecture *via* the introduction of a PEG chain[69] encompasses: 1) an increase in the circulation time of the dendrimer in the blood; 2) an increase in the concentration of the dendrimer and the loaded drug in the tumor *via* the passive EPR effect, which is a challenge at present.[70] Importantly, less than 2% of the drug reaches the tumor site.[71,72] The importance of patient selection for nanodevice development has been highlighted.[73] An additional pathway to deliver to tumors was recently proposed, known as the active transcytosis effect.[74]

The introduction of a chain between the loaded drug and the surface of the dendrimer allows: 1) gradual hydrolytic drug release; 2) increase in the drug elimination half-life, the major requirement for the EPR process; 3) increase of the PK/PD profile of the loaded drugs. The formation of leaky vasculatures in tumors may explain the EPR effect, based on poorly-aligned endothelial cells and large fenestrations. Nevertheless, the EPR effect as a universal process in nanomedicine has been recently questioned. As discussed by Cabrala and Kataoka[75] and by Ngoune and colleagues,[76] the heterogeneity of the vasculature and the permeability of tumors modify the perfusion and distribution of NPs within the tumor mass, and this effect may be rendered uneven. A harsh verdict was reached, namely that the EPR effect exhibited more in rodents than in humans. [71]

4.5. Near-infinite possibilities, but few examples, for the use of dendrimers as drugs themselves based on first-in-class drug development strategy

The other direction in nanomedicine is to develop dendrimers as drugs alone, *i.e.*, as active drugs *per se*. Figure 9 depicts several examples of therapeutic usage of dendrimers as drugs. It is important to note that several biocompatible dendrimer types showed good *in vivo* activities as anticancer agents, including PAMAM dendrimers[58] and some types were demonstrated as anti-inflammatory agents, including phosphorus dendrimers[34] and carbosilane dendrimers. [77,78]

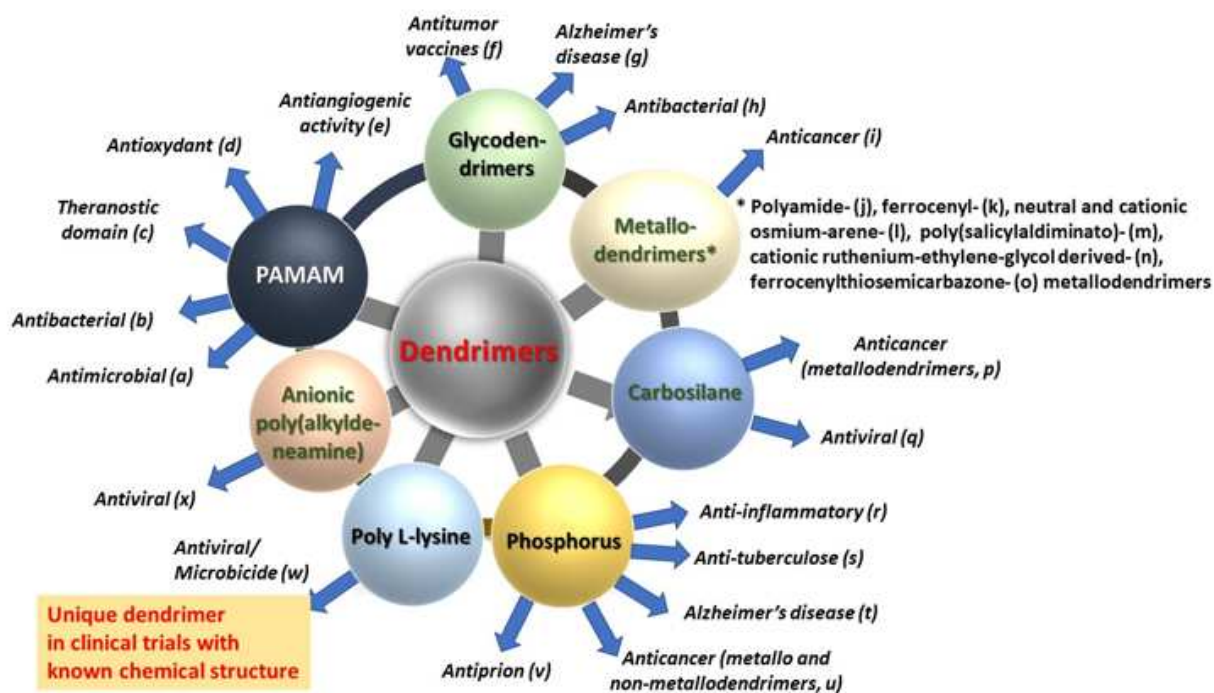


Figure 9. Dendrimers used in therapeutic domains as drugs. For representative examples : a[79], b[80], c[81], d[82], e[83], f[84], g[85], h[86], i[87], j[88], k[89], l[90], m[91], n[92], o[93], p[77], q[94], r[95, 96], s[97], t[98], u[99],v[100], w[101], x[102]

5. Marketed and clinical dendrimers in nanomedicine

To the best of our knowledge, two activated amino dendrimers were developed for cell transfection application, by compacting negatively-charged DNA/siRNA and increasing its uptake into cells encompassing fibroblast and epithelial cells. Superfect (Qiagen, USA) and Priostar (EMD/Merck Biosciences/Starpharma) were commercialized, as were VivaGel condoms (Strapharma, Australia) as contraceptive agent (*vide infra*).

5.1. Dendrimers in the clinical realm: very few examples to date!

For a medicinal chemist, the holy grail is to design and introduce a compound in the clinical phase and then market it as a drug to treat patients. In spite of the large amount of research carried out over decades, few dendrimers have crossed the milestone of entering the clinic. In the dendrimer field, the pharmaceutical company Starpharma Holdings Ltd (Melbourne, Australia) succeeded in introducing dendrimers, as first-in-class NPs, in clinical trials. This development started from the preparation of G4 PAMAM dendrimer-based polyanions SPL2923 and SPL6195 (Figure 10), showing *in vitro* antiviral activity of against a range of HIV-1 strains, with EC₅₀ ranging between 0.08 and 0.7 µg/m: in MT-4 and PBMC cells. SPL2923 and SPL6195 were shown to act on virus attachment and fusion similarly to the sulfated carbohydrate dextran sulfate (DS).[101]

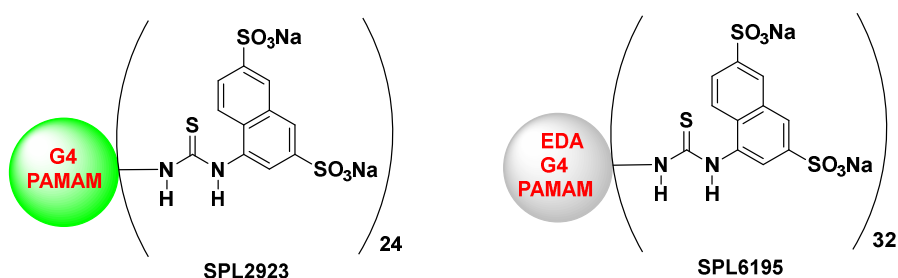


Figure 10. Chemical structure of SPL2923 and SPL6195

One of the first decisions of Starpharma was to focus on HIV prevention vs. treatment, based on 2002 HIV epidemic statistics. Their lead optimization strategy allowed the preparation of three original dendrimer types of generation 3, L-lysine, PAMAM and PPI, bearing 32 sodium 1-(carboxymethoxy)naphthalene-3,6-disulfonate surface groups. Stabilization analysis, formulation studies and scale-up chemical analysis were conducted to produce SPL7013 for preclinical development, under the brand name Vivagel (Figure 11).[103,104] Around 100 kg of SPL7013 was produced, and a water-based Carbopol gel formulation was selected for clinical trials. In pivotal nonhuman primate (macaques) efficacy studies, a single intravaginal dose of Vivagel showed good protection against simian-human immunodeficiency virus (SHIV).[105] Phase I trials (36 healthy women) displayed good safety[106] and acceptability profile, as well as retention and duration of the activity.[107] In addition, SPL7013 was not absorbed into the systemic circulation following intravaginal dosing.

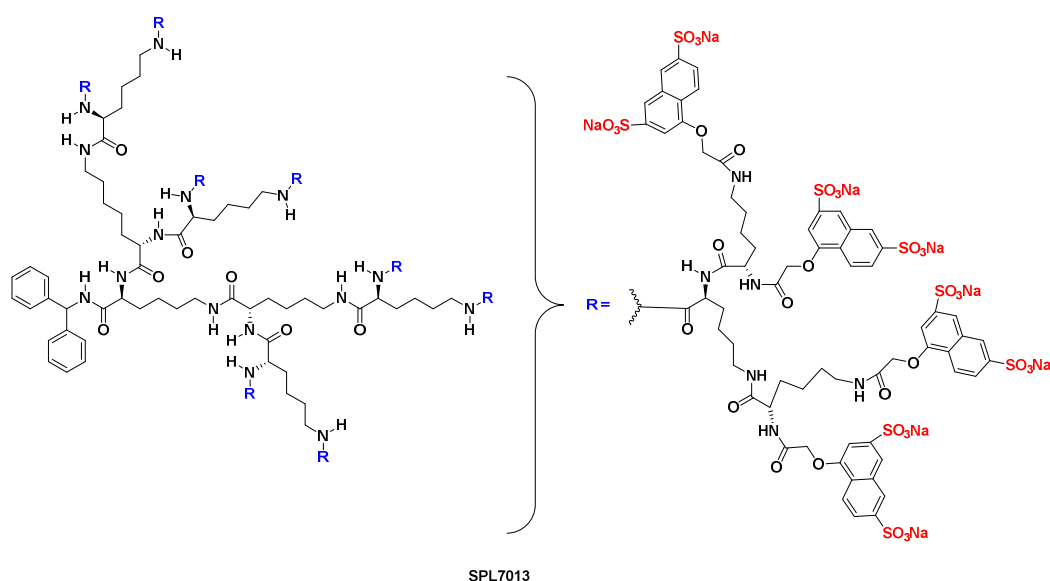


Figure 11. Chemical structure of SPL7013

Phase II double-blind trials demonstrated retention and duration of activity (against HIV and HSV-2), as well as prevention of bacterial vaginosis. VivaGel demonstrated statistically significant efficacy in pivotal Phase III trials (1,223 women, multi centers to treat bacterial vaginosis. VivaGel is being applied to a range of sexual/women's health products by Starpharma and its partners, including in antiviral condoms (Vivagel in lubricant), for the treatment and prevention of bacterial vaginosis (BV) and for the prevention of sexually transmitted infections (STIs). In 2018, Starpharma announced the development of SPL7013

for the treatment and the prevention of microbial infections of the eye, such as, for instance, adenoviral conjunctivitis and bacterial conjunctivitis.[108] Recently, similar to any dynamic pharmaceutical company, Starpharma has increased the range of therapeutic applications of its drugs based on in-house knowledge. Thereby, as indicated before, dendrimers can be used as nanocarriers (best-in-class development strategy) and as drugs (first-in-class development strategy). Starpharma is developing their DEP portfolio combined with anti-cancer agents, including DEP docetaxel, which is a conjugated form of the anti-cancer agent docetaxel (Taxotere) with po-L-lysine dendrimers. Importantly, pre-clinical studies showed that water-soluble DEP docetaxel (chemical structure not disclosed) displayed substantially better efficacy and lower toxicity than Taxotere alone against breast, prostate, lung and ovarian tumor types, with the absence of neutropenia, the major dose-limiting toxicity for Taxotere, which also requires surfactants such as polysorbate 80 for dissolution. DEP docetaxel is cGMP scalable, and is currently in Phase II clinical trials for treating lung cancer and prostate cancer. Starpharma have also investigated the combination of DEP docetaxel with other anticancer agents, such as nintedanib (Vargatef). In addition, Starpharma is developing other DEP products, such as DEP cabazitaxel (Phase II trials, chemical structure not disclosed) and DEP irinotecan (Phase I/II trials, chemical structure not disclosed). In collaboration with AstraZeneca, Starpharma is developing AZ DEP AZD0466, a lysine dendrimer nanopatform conjugating the Astra Zeneca cancer drug AZD4320, which targeting both Bcl2 and Bcl/xL proteins.[108] Very recently, Starpharma announced the development of SPL7013 as a potent antiviral agent against the respiratory syncytial virus (RSV) before and/or after exposure to the virus, using nasal spray technology (VIRALEZE). Expanding studies to other respiratory viruses, including SARS-CoV-2 (the coronavirus causing COVID-19) and influenza, are ongoing.[108]

Along the same lines, Orpheris, Inc. (USA) is developing (double-blind Phase II) the dendrimer *N*-acetylcysteine OP-101 (chemical structure not disclosed) in patients with severe COVID-19, where OP-101 reduced the inflammatory cytokine storm.[109]

5.2. What are the biggest challenges in dendrimer development for dendrimer translation into the clinic?

As a general trend, during drug development, the crucial step is to successfully jump the valley between preclinical studies and the clinic – the so-called ‘Valley of Death’. In the first step, we can analyze the situation in nanomedicine and then transpose this to the field of dendrimers, highlighting similarities and differences. Several authors have discussed the challenges and drawbacks associated with nanomedicine, such as Lagarce, [110] Guidolin and Zheng,[111] Cheng *et al.*,[112] Wu *et al.*[113] and Huynh and Zheng.[114] A highly interesting roadmap report on dendrimers from the European Commission was published, highlighting that dendrimer research is very much application-oriented.[115]

In nanomedicine, in the dendrimer space[116], despite 40 years of research, why there is a plethora of work in preclinical studies compared to very few reports of dendrimer application in the clinical realm? First, we examine the situation in the wider space of nanomedicine. This question also arises in the field of so-called classical medicines. The

challenges to find and develop drugs may be, on occasion, the same as for nanomedicine and dendrimer development.

The first analysis to sound the alarm was published in 2013 by Vendito and Szoka, describing the development of nanomedicines vs. small molecules and monoclonal antibodies in the oncology realm.[117] Two series of analysis were performed, involving chronologically analyzing publications and published papers about clinical trials, 1) *a.* invention phase, *b.* innovation phase, and *c.* imitation phase; and looking at times for the following different phases, 2) *a.* last invention to drug innovation phase, *b.* development phase from innovation to clinical trials, and *c.* clinical trials to the FDA decision phase.

In order to increase the success rate and to bring more drugs into the clinic, the authors suggested, as solutions, that the inventors and innovators obtain funds based on science and drug development, respectively, and specific funds be allocated for imitators. The obtaining of ‘lottery grants’ based on poor ideas must be avoided, and less focus placed on publication records and more on scientific progress that translates into patient treatment. In addition, the authors analyzed the times of innovation phase, development phase and clinical trial phase for seven nanomedicines, including Doxil[®], Abraxane[®], Rituximab[®] (monoclonal anti-CD20 antibody), Mylotarg[®] (Gemtuzumab ozogamicin, antibody-drug conjugate against CD33 antigen, withdrawn 2010), CRXL101 (cyclodextrin polymer containing camptothecin), MM398 (nanoliposomal Irinotecan), and EZN 2208 (polyethylene glycol drug conjugate of SN38). The amount of time taken for each of these nanomedicines from invention to clinical trials and approval is related to several factors, including the level of innovation and the time to concretely develop the innovation, the difficulties in its development, and, finally, the clinical trials. Doxil[®] and Abraxane[®] showed shorter innovation time periods over monoclonal antibodies and over the other nanomedicines, which include CRXL101, MM398 and EZN 2208. The drug carriers have a more difficult pathway through the clinic vs. monoclonal antibodies, including Doxil[®] and Abraxane[®], and also *versus* the parent molecules. The authors argued that for ‘*most currently approved drugs, reformulating them in a nanocarrier provides a small increase in performance that large pharmaceutical companies do not consider being worth the time, effort and expense of development*’. We completely share this point of view, which is also true in the field of dendrimers. Only two companies have introduced dendrimers in the field of nanomedicine in the clinic and commercialized several of them: Starpharma/AstraZeneca.

Based on several reviews, including Swenson[118], Guidolinin and Zheng,[111] Sanhai and colleagues,[119] Mignani, Shi, Rodrigues, and Majoral,[120] in Table 1 we present several tailored propositions to solve major identified challenges to be overcome in the development of dendrimers, for their translation into the clinic.

Table 1. Inherent problems to be solved during the development of dendrimers and corresponding tailored solutions.

	Challenges	Tailored propositions
1.	Complex, slow and costly synthesis of the majority of tailored dendrimer types for specific medical applications – the greater the generation, the greater the difficulties in synthesis, purification, as well as	Synthesis of low-generation and chemically stable dendrimers Use of orthogonal chemistry approaches[121]

	chemical instability.	
	Monodispersity and chemical and biological (<i>e.g.</i> , in the blood, renal and hepatic clearances) stabilities of dendrimers	Consider important criteria for clinical development as well as chemical stability Analyze and characterize dendrimers that are crucial for the development
	Fundamental researches	Develop fundamental research[41] on dendrimers to better understand their potential in nanomedicine for translation into the clinic Conduct more systemic investigations and collect more data on the PD and PK behaviors of dendrimers Address non-standard formulation issues to improve the biodistribution of dendrimers Motivation from the scientists to develop new backbones, morphologies, hybridation of dendrimers with other complex structures
	Unmet medical need	Focus initial research on specific medical needs/indications (<i>e.g.</i> , rare diseases, difficult-to-treat diseases) Focus research on personalized nanomedicine, based on patient-specific factors, to become a standard of care Use diagonal translation strategy for several therapeutic applications (<i>vide infra</i>)[111]
	Attractiveness vs. other nanocarriers, such as liposomes and polymeric NPs	Promote a better 'quality/druggability' profile as nanocarriers and active drugs <i>per se</i> with lower development cost over other NPs used in the clinic. Avoid a cul-de-sac situation – do not embark on too difficult a project to be fully completed in due time (<i>e.g.</i> , too-complex multifunctional dendrimers). Keep it simple as much as possible and think out of the box.
	Reproducible scale-up synthesis under GMP grade and manufacturing	Develop reproducible scale-up synthesis of dendrimers under GMP grade is mandatory for clinical use. The simpler the chemical structure of the dendrimer is, the higher the probability of success Enact GMP scale-up, not simple production processes, for large batch production of dendrimers to be analyzed in an early stage based on the success of lipid nanocapsules.[122] Address manufacturing problems
	Translational nanomedicine	Learn from translational experience with recently-approved NPs, such as antibody-

		drug conjugates (ADC)[123] Develop precision theranostic field with dendrimers[124]
	Convincing regulatory agencies (Food Drug Administration (FDA) and European Medicines Agency (EMA)) to develop dendrimers in nanomedicine	Have strong advantages <i>versus</i> current treatments with biocompatible dendrimers
	Convincing academic dendrimer researchers to be more like 'medicinal chemists', and to develop dendrimers as nanomedicines	Enact successful cooperation (collective efforts) between experts in biology, chemistry, nanotechnology, medical and pharmacological communities and clinical research, as well with pharmaceutical companies which that are experts in drug development Capitalize on the strengths of each partner Collect and share information from academia and industry, and set up a standard process based on practical checkpoints[11]
	Convince the pharmaceutical companies (small[125] and large) to develop dendrimers in nanomedicines and change over their tactical de-risking policy	Develop biocompatible dendrimers showing an advantage <i>vs.</i> other internal 'competitors' in the pipeline of pharmaceutical companies. Prioritize development of first-in-class dendrimers (<i>e.g.</i> , as active drugs <i>per se</i>) over best-in-class (nanocarriers) Boost clinical translation based on strong cooperation For early-stage development, improve connection with investors

6. Conclusion and prospects

From the vastness of the dendrimer space in nanomedicine, and in line with our different research projects, in this original review, we survey the recent analysis of attributes and challenges of dendrimers to move forward into the clinic. We are convinced that the tailored and rational design of dendrimers as nanocarriers to control the delivery of drugs and as active drugs *per se* for therapeutic and diagnostic purposes (theranostic realm) should be achieved by a better understanding of the basic aspects of dendritic systems, as well as of their pharmacokinetics profiles for elongating their effective therapy.

At this point, what is the next dendrimer type to be coined?

As discussed and analyzed previously, and based on the principle of *clinical multifunctionality* profile proposed by Guidolinin and Zheng,[111] Table 2 presents a selection of nanoparticles used in the oncology domain and as microbicides, classified based on their best-in-class and first-in-class profiles and their respective multiplicity design and

clinical multifunctionality profiles. The first marketed microbicide dendrimer VivaGel® is also included in this table. Multiplicity design refers to the multifunctional design of NPs, whereas the clinical multiplicity profile is the use of NPs for multiple clinical applications or benefits. For example, Abraxane® is a simple albumin-bound paclitaxel (no multifunctionality, No), but it has been applied to solve many clinical problems (Yes), such as breast and lung and pancreatic cancers. On the other hand, Vyxeos® (liposomal daunorubicin and cytarabine) is multifunctional (Yes) on the nanoscale. However, it solves a single clinical problem (AML), so its clinical multifunctionality is No. FeraMAX® (a polysaccharide iron complex supplement) has no multifunctional profile. However, because it is used both as a diagnostic agent for imaging and as a therapeutic for treating iron-deficiency anaemia, its clinical multifunctionality is Yes. It is interesting to note that the clinical multiplicity profile for one specific NP could change during its development in the clinic from one therapeutic application (No) to several therapeutic applications (Yes). This process has been also defined and named diagonal translation by Guidolinin and Zheng,[111].

We are strongly convinced, as Starpharma, the development of first-in-class dendrimers active per se represents the future in the treatment of difficult diseases such pancreatic, stomach, brain and skin cancer, and to end the decrease in drug discovery productivity observed in recent years. Let us not forget that our unique objective is to design NPs in general and dendrimers in particular to fight diseases in humans. Working on the frontiers of dendrimer science in the nanomedicine, scientists in nanomedicine weigh in on the future of the drug pipeline, as mentioned by Trigg like astronauts to explore the enormous chemistry potential to find new drugs in the universe. [126]

Arguably, we are also convinced that ‘only one leg’ dendrimer development may not be the future in nanomedicine. The salient future will be the development of biologically active dendrimers as bridges to other *biocompatible* polymeric architectures to tackle difficult disease.

Table 2. Selection of NPs based on best-in-class and first-in-class properties and their respective multifunctionality design and clinical multifunctionality profiles.

First-mover (pioneer) and second mover (follower)	Multifunctionality design	Clinical multifunctionality profile	Relevant examples of NPs in clinic to tackle cancers and as microbicides
Best-in-class	No	No	Eligard®, Marquibo®, Onivyde®, Doxil®
	No	Yes	Abraxane®, FeraMax®, Megace ES®, DEP docetaxel® (dendrimer as nanocarrier), DEP cabazitaxel® (dendrimer as nano carrier)*
	Yes	No	Vyxeos®
	Yes	Yes	No example
First-in-class	No	No	Oncaspar®
	No	Yes	Mylotarg® (ADC), VivaGel®

* Based on Phase II clinical trials[108]

We are also convinced that the development of dendrimers as active drugs *per se* opens a new route strategy to find an original molecular mechanism of action of these NPs based on the principle of ligandability space, related to the nature of ligands target types and ligandability. This principle has been highlighted by the company Arvinas[127] and by Ottl *et al.*[128] (Figure 12). In line with our research, this principle has been observed by us regarding the development of the first-in-class metallodendrimers, particularly in the case of metallo-conjugated phosphorus dendrimers (1G3-Cu), bearing Cu(II) on their surface that shows noteworthy antiproliferative activities through the apoptotic process. We found these series of original metallodendrimers using phenotypic screening of a library of G1-G3 phosphorus dendrimers against a panel of tumor cell lines. An original molecular mechanism of action has been observed (*in vitro* and *in vivo* experiments): **1G3-Cu** strongly translocates the pro-apoptotic Bax protein, inducing apoptosis.[129, 130] This strategy provide grist to the mills for the development of first-in-class dendrimers based on phenotypic screening. Importantly, in precision theranostic field, as demonstrated by Shi *et al.*[131] the **1G3-Cu** copper(II)-conjugate phosphorus dendrimers were highly taken down *in vivo* cancers through non-invasive UTMD (ultrasound-targeted microbubble destruction) technique to promote the magnetic resonance (MR) imaging and chemotherapy of the pancreatic tumor (SW1990 cells).

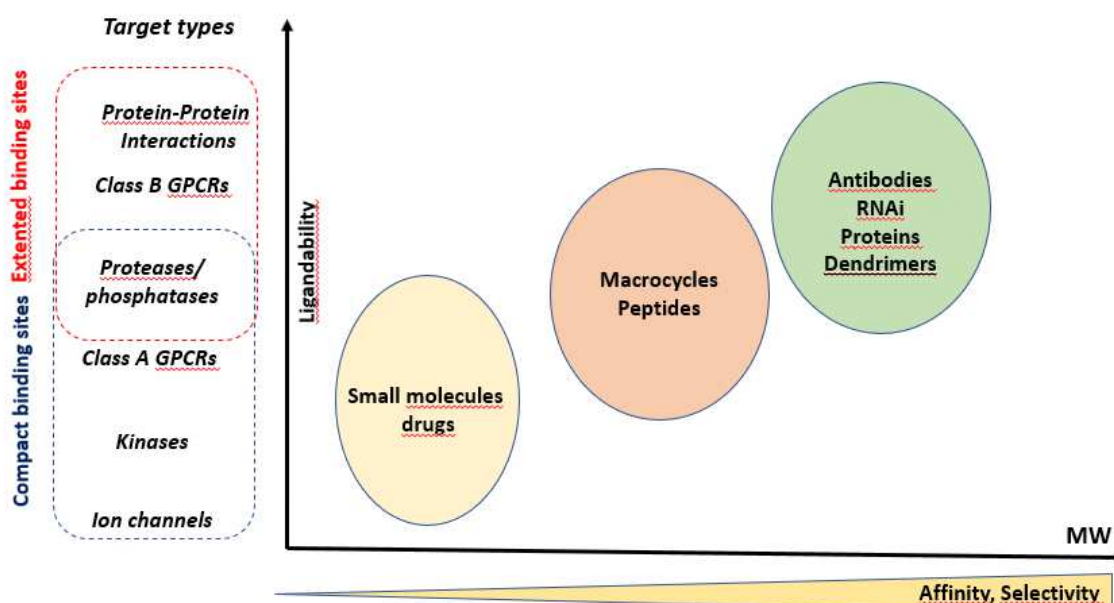


Figure 12. Chemical space available versus target types and ligandability

ORCID

Serge Mignani : 0000-0002-1383-5256

Xiangyang Shi : 0000-0001-6785-6645

Jean-Pierre Majoral : 0000-0002-0971-817X

João Rodrigues : 0000-0003-4552-1953

Helena Tomas : 0000-0002-7856-2041

Andreii Karpus : 0000-0002-5760-3086

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

X. Shi, S. Mignani and J-P. Majoral thank the PRC NSFC-CNRS 2019 (21911530230 for X.S. and 199675 for S.M. and J-P.M). S. Mignani, J. Rodrigues, H. Tomás and X. Shi acknowledge the support of FCT-Fundação para a Ciência e a Tecnologia (Base Fund UIDB/00674/2020 and Programmatic Fund UIDP/00674/2020, Portuguese Government Funds) and ARDITI-Agência Regional para o Desenvolvimento da Investigação Tecnologia e Inovação through the project M1420-01-0145-FEDER-000005-CQM+ (Madeira 14-20 Program). J. P. Majoral thanks CNRS (France) for financial support. J. P. Majoral, S. Mignani and A. Karpus acknowledge the support of EuroNanoMed III Project (European Union's Horizon 2020 research and innovation programme under grant agreement no 723770). We would like to thank Prof. G. Zheng and Prof. K. Guidolin (Department of Surgery, University of Toronto, Toronto, Canada) for the very fruitful discussions on the concept of clinical multifunctionality and diagonal translation.

7. References

1. Kargozara, S.; Mozafari, M., Nanotechnology and Nanomedicine: Start small, think big. *Materials Today: Proceedings* **2018**, *5*.
2. Pasut, G., Grand challenges in nano-based drug delivery. *Frontiers in Medicinal technology* **2019**, *1*, 1-4.
3. Yohan, D.; Chithran, B. D., Applications of Nanoparticles in Nanomedicine. *J. Biomed. Nanotechnol.* **2014**, *10*, 2371-2392.
4. Seleci, M.; Ag Seleci, D.; Jonczyk, R.; Stahl, F.; Blume, C.; Scheper, T., Smart multifunctional nanoparticles in nanomedicine. *BioNanoMaterials* **2016** *17*, 33–41.
5. Phillips, M. I.; Lee, J. R., Recent orphan drugs that are first-in class. *Expert Opinion on Orphan Drug* **2014**, *2*, 759-763.
6. Luscombe, E., Is being the first ever 'better' than being the best?., *Expert Opinion on Pharmacotherapy* **2014**, *15*, i-ii.
7. LaMattina, J., *Forbes website. Available from: <http://www.forbes.com/sites/johnlamattina/2013/06/17/bcg-weighs-in-on-first-inclass-vs-best-in-class-drugs-how-valuable-is-their-advice/>, [Accessed December 2020].*
8. Eder, J.; Sedrani, R.; Wiesmann, C., The discovery of first-in-class drugs: origins and evolution. *Nat. Rev. Drug Discov.* **2014**, *13*, 577-587.
9. Schulze, U.; Ringel, M., What matters most in commercial success: first-in-class or best-in-class? *Nat. Rev. Drug Discov.* **2013**, *12*, 419-420.
10. Swinney, D. C., Phenotypic vs. target-based drug discovery for first-in-class medicines. *Clin. Pharmacol. Ther.* **2013**, *93*, 299-301.
11. Choi, Y. H.; Han, H. K., Nanomedicines: Current Status and Future Perspectives in Aspect of Drug Delivery and Pharmacokinetics. *J. Pharm. Invest.* **2018**, *48*, 43-60.
12. Santos, A.; Veiga, F.; Figueiras, A., Dendrimers as Pharmaceutical Excipients: Synthesis, Properties, Toxicity and Biomedical Applications. *Materials* **2020**, *13*, 65.

13. Hejmady, S.; Pradhan, R.; Alexander, A.; Agrawal, M.; Singhvi, G.; Gorain, B.; Tiwari, S.; Kesharwani, P.; Kumar Dubey, S. K., Recent advances in targeted nanomedicine as promising antitumor therapeutics. *Drug Discov. Today* **2020**, <https://doi.org/10.1016/j.drudis.2020.09.031>.
14. Khandare, J.; Calderon, M.; Dagia, N. M.; Haag, R., Multifunctional dendritic polymers in nanomedicine: opportunities and challenges. *Chem. Soc. Rev.* **2012**, *41*, 2824-2848.
15. Thakor, P.; Bhavana, V.; Sharma, R.; Srivastava, S.; Singh, S. B.; Mehra, N. K., Polymer–drug conjugates: recent advances and future perspectives. *Drug Discov. Today* **2020**, *25*, 1718-1726.
16. Singh, R.; Lillard, J. W., Nanoparticle-based targeted drug delivery. Experimental and molecular pathology. **2009**, *86*, 215-223.
17. Selec, M.; Selec, D. A.; Jonczyk, R.; Stahl, F.; Blume, C.; Scheper, T., Smart multifunctional nanoparticles in nanomedicine *BioNanoMaterials* **2015**, *17*, 1-2.
18. Kargozara, S.; Mozafari, M., Nanotechnology and Nanomedicine: Start small, think big *Materials Today: Proceedings* **2018**, *5*, 15492–15500
19. Reddy, H.; Couvreur, P., Nanotechnology for therapy and imaging of liver diseases. *J. Hepatol.* **2011**, *55*, 1461-1466.
20. CADTH COMMON DRUG REVIEW. Treatment of polyneuropathy in adult patients with hereditary transthyretin-mediated amyloidosis. https://www.ncbi.nlm.nih.gov/books/NBK549757/pdf/Bookshelf_NBK549757.pdf [Accessed December 2020].
21. Duggan, S. T.; Keating, G. M., Pegylated liposomal doxorubicin: a review of its use in metastatic breast cancer, ovarian cancer, multiple myeloma and AIDS-related Kaposi's sarcoma. *Drugs* **2011**, *71*, 2531-2558.
22. Hau, P.; Fabel, K.; Baumgart, U.; Rümmele, P.; Grauer, O.; Bock, A.; Dietmaier, C.; Dietmaier, W.; Dietrich, J.; Dudel, C.; Hübner, F.; Jauch, T.; Drechsel, E.; Kleiter, I.; Wismeth, C.; Zellner, A.; Brawanski, A.; Steinbrecher, A.; Marienhagen, J.; Bogdahn, U., Pegylated liposomal doxorubicin - efficacy in patients with recurrent high - grade glioma. *Cancer* **2004**, *100*, 1199-1207.
23. Ma, P.; Mumper, R. J., Paclitaxel Nano-Delivery Systems: A Comprehensive Review. *J. Nanomed. Nanotechnol.* **2013**, *4*, 1000164.
24. Buhleier, E.; Wehner, W.; Vögtle, F., Cascade and Nonskid-Chain-Like Syntheses of Molecular Cavity Topologies. *Synthesis* **1978**, *2*, 155–158.
25. Tomalia, D. A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, K.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P., A New Class of Polymers: Starburst-Dendritic Macromolecules. *Polym. J.* **1985**, *17*, 117–132.
26. Mignani, S.; Rodrigues, J.; Roy, R.; Shi, X.; Ceña, V.; El Kazzouli, S.; Majoral, J.-P., Exploration of biomedical dendrimer space based on in-vitro physicochemical parameters: key factor analysis (Part 1). *Drug Discov. Today* **2019**, *24*, 1176-1183.
27. Mignani, S.; Rodrigues, J.; Roy, R.; Shi, X.; Cena, V.; El Kazzouli, S.; Majoral, J.-P., Exploration of biomedical dendrimer space based on in-vivo physicochemical parameters: Key factor analysis (Part 2). *Drug Discov. Today* **2019**, *24*, 1184-1192.
28. Fukuda, T., Biological recognition at interfaces involving dendritic molecules. *Polym. J.* **2019**, *51*, 535–546.
29. Hsu, H. J.; Bugno, J.; Lee, S. R.; Hong, S., Dendrimer-based nanocarriers: A versatile platform for drug delivery. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol* **2017**, *9*, e1409.
30. Augustus, E. N.; Allen, E. T.; Nimibofa, A.; Donbebe, W., A review of synthesis, characterization and applications of functionalized dendrimers. *Am. J. Polym. Sci.* **2017**, *7*, 8–14.
31. Maraval, V.; Caminade, A. M.; Majoral, J.-P.; Blais, J. C., Dendrimer design: How to circumvent the dilemma of a reduction of steps or an increase of function multiplicity? *Angew. Chem. Int. Ed.* **2003**, *42*, 1822-1826.
32. Lu, Y.; Nemoto, T.; Tosaka, M.; Yamago, S., Synthesis of structurally controlled hyperbranched polymers using a monomer having hierarchical reactivity. *Nat. Commun* **2017**, *8*, 1863.

33. Elsabahy, M.; Wooley, K. L., Design of polymeric nanoparticles for biomedical delivery applications. *Chem. Soc. Rev.* **2012**, *41*, 2545–2561.
34. Caminade, A. M.; Turrin, C. O.; Majoral, J. P., Phosphorous dendrimers in biology and nanomedicine: Syntheses, characterization, and properties. *Jenny Stanford Publishing* **2018**.
35. Schlenk, C.; Frey, H., Carbosilane dendrimers-Synthesis, functionalization, application. *Monatsh Chem.* **1999**, *130*, 3–14.
36. Choi, J. S.; Joo, D. K.; Kim, C. H.; Kim, K.; Park, J. S., Synthesis of a Barbell-like Triblock Copolymer, Poly(l-lysine) Dendrimer-block-Poly(ethylene glycol)-block-Poly(l-lysine) Dendrimer, and Its Self-Assembly with Plasmid DNA. *J. Am. Chem. Soc.* **2000**, *122*, 474–480.
37. David Pahovnik, D.; Čusak, A.; Reven, S.; Žagar, E., Synthesis of poly(ester - amide) dendrimers based on 2,2 - Bis(hydroxymethyl) propanoic acid and glycine. *J. Polym. Sci., Part A: Polym. Chem.* **2014**, *52*, 3292 – 3301.
38. KristenSadler, K.; Tam, J. P., Peptide dendrimers: applications and synthesis. *Mol. Biotechnol.* **2020**, *90*, 195-229.
39. Zhang, X.; Zhang, Z.; Xu, X.; Li, Y. Y.; Li, Y. Y.; Jian, Y.; Gu, Z., Bioinspired therapeutic dendrimers as efficient peptide drugs based on supramolecular interactions for tumor inhibition. *Angew. Chem. Int. Ed. Engl.* **2015**, *27*, 4289-4294.
40. Mignani, S.; El Kazzouli, S.; Bousmina, M.; Majoral, J.-P., Expand classical drug administration ways by emerging routes using dendrimer drug delivery systems: A Concise overview. *Adv. Drug Delivery Rev.* **2013**, *35*, 1316-1330.
41. Kannan, R. M.; Nance, E.; Kannan, S.; Tomalia, D. A., Emerging concepts in dendrimer-based nanomedicine: from design principles to clinical applications. *J. Intern. Med.* **2014**, *276*, 579-617.
42. Janaszewska, A.; Lazniewska, J.; Trzepiński, P.; Marcinkowska, M.; Klajnert-Maculewicz, B., Cytotoxicity of dendrimers. *Biomolecules* **2019**, *9*, 330.
43. Parat, A.; Bordeianu, C.; Dib, H.; Garofalo, A.; Walter, A.; Bégin-Colin, S.; Felder-Flesch, D., Dendrimer-nanoparticle conjugates in nanomedicine. *Nanomedicine (Lond)* **2015**, *10*, 977-992.
44. Lee, C. C.; MacKay, J. A.; Fréchet, J. M.; Szoka, F. C., Designing dendrimers for biological applications. *Nat. Biotechnol.* **2005**, *23*, 1517-1526.
45. Ciolkowski, M.; Petersen, J. F.; Ficker, M.; Janaszewska, A.; Christensen, J. B.; Klajnert, B.; Bryszewska, M., Surface modification of PAMAM dendrimer improves its biocompatibility. *Nanomed. Nanotechnol. Biol. Med.* **2012**, *8*, 815–817.
46. Aurelia Chis, A. A.; Dobrea, C.; Claudiu Morgovan, C.; Arseniu, A. M.; Rus, L. L.; Butuca, A.; Juncan, A. M.; Totan, M.; Vonica-Tincu, A. L.; Cormos, G.; Muntean, A. C.; Muresan, M. L.; Gligor, F. G.; Frum, A., Applications and Limitations of Dendrimers in Biomedicine. *Molecules* **2020**, *25*, 3982.
47. Moghimi, S. M.; Simberg, D., Nanoparticle transport pathways into tumors. *J. Nanopart. Res.* **2018**, *20*, 169.
48. Wijagkanalan, W.; Kawakami, S.; Hashida, M., Designing Dendrimers for Drug Delivery and Imaging: Pharmacokinetic Considerations. *Pharm. Res.* **2011**, *28*, 500–1519.
49. Kaminskis, L. M.; Boyd, B. J.; Porter, C. J. H., Dendrimer pharmacokinetics: the effect of size, structure and surface characteristics on ADME properties. *Nanomedicine* **2011**, *6*, 1063–1084.
50. Cheng, Y. Y.; Wang, J. R.; Rao, T. L.; He, X. X.; Xu, T. W., Pharmaceutical applications of dendrimers: promising nanocarriers for drug delivery. *Front. Biosci.* **2008**, *13*, 1447-1471.
51. Maciejewski, M., Concepts of trapping topologically by shell molecules. *Macromol. Sci. Chem. A* **1982**, *17*, 689-703.
52. Chauhan, A. S., Dendrimers for drug delivery. *Molecules* **2018**, *23*, 938.
53. Markowicz-Piasecka, M.; Mikiciuk-Olasik, E., Dendrimers in drug delivery. *Nanobiomaterials in Drug Delivery Applications of Nanobiomaterials* **2016**, *9*, 39-74.

54. Noriega-Luna, B.; Godínez, L. A.; Rodríguez, F. J.; Rodríguez, A.; de Larrea, G. Z.-L.; Sosa-Ferreyra, C. F.; Mercado-Curiel, R. F.; Manríquez, J.; Bustos, E., Applications of Dendrimers in Drug Delivery Agents, Diagnosis, Therapy, and Detection. *J. Nanomater.* **2014**, Article ID 507273,.
55. Ihre, H. R.; de Jesús, O. L. P.; Szoka, F. C.; Fréchet, J. M. J., Polyester dendritic systems for drug delivery applications: Design, synthesis, and characterization. *Bioconjug. Chem.* **2020**, *13*, 443–452.
56. Marquez-Miranda, V.; Araya-Duran, I.; Gonzalez-Nilo, F. D., Multiscale molecular simulations applied to nucleic acid-dendrimer interactions studies. *Curr. Pharm. Des.* **2017**, *23*, 3062-3075.
57. Gajbhiye, V.; Palanirajan, V. K.; Tekade, R. K.; Jain, N. K., Dendrimers as therapeutic agents: a systematic review. *JPP* **2009**, *61*, 989–1003.
58. Mignani, S.; Majoral, J.-P., Dendrimers as macromolecular tools to tackle from colon to brain tumor types : a concise overview. *New. J. Chem.* **2013**, *37*, 3337-3357.
59. Xiong, Z.; Shen, M.; Shi, X., Dendrimer-based strategies for cancer therapy: Recent advances and future perspectives. *Sci. China Mater.* **2018**, *61*, 1387–1403.
60. Mignani, S.; Rodrigues, J.; Tomas, H.; Zablocka, M.; Shi, X.; Caminade, A. M.; Majoral, J.-P., Dendrimers in combination with natural products and analogues as anti-cancer agents. *Chem. Soc. Rev.* **2018**, *47* (), 514-532.
61. Shcharbin, D.; Janaszewska, A.; Klajnert-Maculewicz, B.; Ziembra, B.; Dzmitruk, V.; Halets, I.; Loznikova, S.; Shcharbina, N.; Milowska, K.; Ionov, M.; Shakhbazau, A.; Bryszewska, M., How to study dendrimers and dendriplexes III. Biodistribution, pharmacokinetics and toxicity in vivo. *J. Control. Release* **2014**, *181*, 40-52.
62. Mignani, S.; Shi, X.; Zablocka, M.; Majoral, J.-P., Dendrimer-Enabled Therapeutic Antisense Delivery Systems as Innovation in Medicine. *Bioconjugate Chem.* **2019**, *30*, 1938–1950.
63. Mignani, S.; Shi, X.; Ceña, V.; Majoral, J.-P., Dendrimer - and polymeric nanoparticle - aptamer bioconjugates as nonviral delivery systems: a new approach in medicine. *Drug. Disc. Today* **2020**, *25*, 1065-1073.
64. Kurtoglu, Y. E.; Mishra, M. K.; Kannan, S.; Kannan, R. M., Drug release characteristics of PAMAM dendrimer-drug conjugates with different linkers. *Int. J. Pharm.* **2010**, *384*, 189–194.
65. Kamaruzzaman, N. F.; Tan, L. P.; Hamdan, R. H.; Choong, S. S.; Wong, W. K.; Gibson, A. J.; Chivu, A.; Pina, M. D. F., Antimicrobial polymers: The potential replacement of existing antibiotics? *Int. J. Mol. Sci.* **2019**, *20*, 2747.
66. Mhlwatika, Z.; Aderibigbe, B., Application of dendrimers for the treatment of infectious diseases. *Molecules* **2018**, *23*, 2205.
67. Liu, J.; Gu, C.; Cabigas, E. B.; Pendergrass, K. D.; Brown, M. E.; Luo, Y.; Davis, M. E., Functionalized dendrimer-based delivery of angiotensin type 1 receptor siRNA for preserving cardiac function following infarction. *Biomaterials* **2013**, *34*, 3729–3736.
68. Cheng, Y.; Xu, T., The effect of dendrimers on the pharmacodynamic and pharmacokinetic behaviors of non-covalently or covalently attached drugs. *Eur. J. Med. Chem.* **2008**, *43*, 2291-2297.
69. Guillaudeu, S. J.; Fox, M. E.; Haidar, Y. M.; Dy, E. E.; Szoka, F. C.; Fréchet, J. M., PEGylated Dendrimers with Core Functionality for Biological Applications. *Bioconjug. Chem.* **2008**, *19*, 461–469.
70. Prabhakar, U.; Maeda, H.; Jain, R. K.; Sevick-Muraca, E. M.; Zamboni, W.; Farokhzad, O. C.; Barry, S. T.; Gabizon, A.; Grodzinski, P.; Blakey, D. C., Challenges and key considerations of the enhanced permeability and retention effect for nanomedicine drug delivery in oncology. *Cancer Res* **2013**, *15*, 2412-2417.
71. Danhier, F., To exploit the tumor microenvironment: Since the EPR effect fails in the clinic, what is the future of nanomedicine? *J. Control. Release* **2016**, *244*, 108-121.
72. Florence, A. T., Nanotechnologies for site specific drug delivery: Changing the narrative. *Int. J. Pharm.* **2018**, *15*, 1-7.

73. Alddien Natfji, A.; Ravishankar, D.; Osborn, H. M. I.; Greco, F., Parameters Affecting the Enhanced Permeability and Retention Effect: The Need for Patient Selection. *J. Pharm. Sci.* **2017**, *106*, 3179-3187.
74. Pandit, S.; Dutta, D.; Nie, S., Active transcytosis and new opportunities for cancer nanomedicine. *Nature Materials* **2020**, *19*, 478-480
75. Cabral, H.; Kataoka, K., Progress of drug-loaded polymeric micelles into clinical studies. *J. Controlled Release* **2014**, *190*, 465-476.
76. Ngoune, R.; Peters, A.; von Elverfeldt, D.; Winkler, K.; Pütza, G., Accumulating nanoparticles by EPR: A route of no return. *J. Contr. Rel.* **2016**, *238*, 58-70.
77. Carloni, R.; del Olmo, N. S.; Ortega, P.; Fattori, A.; Gómez, R.; Ottaviani, M. F.; García-Gallego, S.; Cangiotti, M.; de la Mata, F. J., Exploring the Interactions of Ruthenium (II) Carbosilane Metallodendrimers and Precursors with Model Cell Membranes through a Dual Spin-Label Spin-Probe Technique Using EPR. *Biomolecules* **2019**, *9*, 540.
78. Sanz del Olmo, N.; Carloni, R.; Bajo, A. M.; Ortega, P.; Gómez, A. F. R.; Ottaviani, M. F.; García-Gallego, S.; Cangiotti, M.; de la Mata, F. J., Insight into the antitumor activity of carbosilane Cu(II)-metallodendrimers through their interaction with biological membrane models. *Nanoscale* **2019**, *11*, 13330-13342.
79. Holmes, A. M.; Heylings, J. R.; Wan, K. W.; Moss, G. P., Antimicrobial efficacy and mechanism of action of poly(amidoamine) (PAMAM) dendrimers against opportunistic pathogens. *Int. J. Antimicrob. Agents* **2019**, *53*, 500-507.
80. Wang, B.; Navath, R. S.; Menjoge, A. R.; Balakrishnan, B.; Bellair, R.; Daia, H.; Romero, R.; Kannan, S.; Kannan, R. M., Inhibition of bacterial growth and intramniotic infection in a guinea pig model of chorioamnionitis using PAMAM dendrimers. *Int. J. Pharm.* **2010**, *395*, 298-308.
81. Ye, M.; Qian, Y.; Tang, J.; Hu, H.; Sui, M.; Shen, Y., Targeted biodegradable dendritic MRI contrast agent for enhanced tumor imaging. *J. Control. Release* **2013**, *169*, 239-245.
82. Esumi, K.; Houdatsu, H.; Yoshimura, T., Antioxidant action by gold-PAMAM dendrimer nanocomposites. *Langmuir* **2004**, *30*, 2536-2538.
83. Shukla, R.; Thomas, T. P.; Peters, J.; Kotlyar, A.; Myc, A.; Baker, J. R., Tumor angiogenic vasculature targeting with PAMAM dendrimer-RGD conjugates. *Chem. Commun.* **2005**, 5739.
84. Chieh Shiao, T.; René Roy, R., Glycodendrimers as functional antigens and antitumor vaccines. *New J. Chem.* **2012**, *36*, 324-339.
85. Klementieva, O., Glycodendrimers as Potential Multitalented Therapeutics in Alzheimer's Disease. *Open access peer-reviewed chapter* **2019**, DOI: 10.5772/intechopen.88974.
86. Teo, I.; Toms, S. M.; Marteyn, B.; Barata, T. S.; Simpson, P.; Johnston, K. A.; Schnupf, P.; Puhar, A.; Bell, T.; Tang, C.; Zloh, M.; Matthews, S.; Rendle, P. M.; Sansonetti, P. J.; Shaunak, S., Preventing acute gut wall damage in infectious diarrhoeas with glycosylated dendrimers. *EMBO Mol. Med.* **2012**, *4*, 866-881.
87. Sanz del Olmo, N.; Carloni, R.; Ortega, P.; García-Gallego, S.; de la Mata, J., Chapter One - Metallodendrimers as a promising tool in the biomedical field: An overview. *Adv. Organomet. Chem.* **2020**, *74*, 1-52.
88. Ahamad, T.; Mapolie, S. F.; Alshehri, S. M., Synthesis and characterization of polyamide metallodendrimers and their anti-bacterial and anti-tumor activities. *Med. Chem. Res.* **2012**, *21*, 2023-2031.
89. Baartzes, N.; Szabo, C.; Cenariu, M.; Imre-Lucaci, F.; Dorneanu, S. A.; Fischer-Fodor, E.; Smith, G. S., In vitro antitumor activity of two ferrocenyl metallodendrimers in a colon cancer cell line. *In. Chem. Comm.* **2018**, *98*, 75-79.
90. Govender, P.; Efafe, F.; Makhubela, B. C. E.; Dyson, P. J.; Therrien, B.; Smith, G. S., Neutral and cationic osmium(II)-arene metallodendrimers: Synthesis, characterisation and anticancer activity. *Inorg. Chimica Acta* **2014**, *409*, 112-120.
91. Govender, P.; Sudding, L. C.; Clavel, C. M.; Dyson, P. J.; Therrien, B.; Smith, G. S., The influence of RAPTA moieties on the antiproliferative activity of peripheral-functionalised poly(salicylaldiminato) metallodendrimers. *Dalton Trans.* **2013**, *42*, 1267-1277.

92. Govender, P.; Riedel, T.; Dyson, P. J.; Smith, G. S., Higher generation cationic N,N-ruthenium(II)-ethylene-glycol-derived metallodendrimers: Synthesis, characterization and cytotoxicity. *J. Organomet. Chem* **2015**, 38e44.
93. Khanye, S. D.; Gut, J.; Rosenthal, P. J.; Chibale, K.; Smith, G. S., Ferrocenylthiosemicarbazones conjugated to a poly(propyleneimine) dendrimer scaffold: Synthesis and in vitro antimalarial activity. *J. Organomet. Chem.*, **2011**, 696, , 3296e3300.
94. Sepúlveda-Crespo, D.; Gómez, R.; De La Mata, F. J.; Jiménez, J. L.; Muñoz-Fernández, M. A., Polyanionic carbosilane dendrimer-conjugated antiviral drugs as efficient microbicides: Recent trends and developments in HIV treatment/therapy. *Nanomedicine* **2015**, 11, 1481-1498.
95. Hayder, M.; Poupot, M.; Baron, M.; Nigou, D.; Turrin, C. O.; Caminade, A. M.; Majoral, J. P.; Eisenberg, R. A.; Fournié, J. J.; Cantagrel, A.; Poupot, R.; Davignon, J. L., A phosphorus-based dendrimer targets inflammation and osteoclastogenesis in experimental arthritis. *Sci. Transl. Med.* **2011**, 3 (81), 81ra35.
96. Bohr, A.; Tsapis, N.; Andreana, I.; Chamarat, A.; Foged, C.; Delomenie, C.; Noiray, M.; El Brahmi, N.; Majoral, J.-P.; Mignani, S.; Fattal, E., Anti-Inflammatory Effect of Anti-TNF- α siRNA Cationic Phosphorus Dendrimer Nanocomplexes Administered Intranasally in a Murine Acute Lung Injury Model. *Biomacromolecules* **2017**, 18, 2379-2388.
97. Mignani, S.; Srivastava, K. K.; Tripathi, R. P.; Soam, D.; Chopra, S.; Dasgupta, A.; Mishra, D. P.; Tripathi, V. D.; Majoral, J.-P.; Caminade, A. M., Indian Patent Application, IN 202011002577. **2020**.
98. Milowska, K.; Grochowina, J.; Katir, N.; El. Kadib, A.; Majoral, J.-P.; Bryszewska, M.; Gabryelak, T., Viologen-phosphorus dendrimers inhibit α -synuclein fibrillation. *Mol. Pharmaceutics* **2013**, 10, 1131-1137.
99. Mignani, S.; El Brahmi, N.; El Kazzouli, S.; Laurent, R.; Sonia Ladeira, S.; Caminade, A.-M.; Pedziwiatr-Werbicka, E.; Szewczyk, E. M.; Bryszewska, M.; Bousmina, M. M.; Cresteil, T.; Majoral, J.-P., Original multivalent gold(III) and dual gold(III)-copper(II) conjugated phosphorus dendrimers as potent antitumoral and antimicrobial agents. *Mol. Pharmaceutics* **2017**, 14, 4087-4097.
100. Solassol, J.; Crozet, C.; Perrier, V.; Leclaire, J.; Beranger, F.; Caminade, A. M.; Meunier, B.; Dormont, D.; Majoral, J.-P.; Lehmann, S., Cationic phosphorus-containing dendrimers reduce prion replication both in cell culture and in mice infected with scrapie. *J. Gen. Virol.* **2004**, 85, 1791-1799.
101. McCarthy, T. D.; Karellas, P.; Henderson, S. A.; Giannis, M.; O'Keefe, D. F.; Heery, G.; Paull, J. R. A.; Matthews, B. R.; Holan, G., Dendrimers as Drugs: Discovery and Preclinical and Clinical Development of Dendrimer-Based Microbicides for HIV and STI Prevention. *Mol. Pharmaceut.* **2**, 312-318.
102. Maciel, D.; Guerrero-Beltrán, C.; Ceña-Diez, R.; Tomás, H.; Muñoz-Fernández, M.; Rodrigues, J. M., New anionic poly(alkylideneamine) dendrimers as microbicide agents against HIV-1 infection. *Nanoscale* **2019**, 11, 969-9690.
103. Bernstein, D. I.; Stanberry, L. R.; Sacks, S.; Ayisi, N. K.; Gong, Y. H.; Ireland, J.; Mumper, R. J.; Holan, G.; Matthews, B.; McCarthy, T.; Bourne, N., Evaluations of Unformulated and Formulated Dendrimer-Based Microbicide Candidates in Mouse and Guinea Pig Models of Genital Herpes. *Antimicrob. Agents Chemother.* **2003**, 47, 3784-3788.
104. Tyssen, D.; Henderson, S. A.; Johnson, A.; Sterjovski, J.; Moore, K.; La, J.; Zanin, M.; Souza, S.; Karellas, P.; Giannis, M. P.; Krippner, G.; Wesselingh, S.; McCarthy, T.; Gorry, P. R.; Ramsland, P. A.; Cone, R.; Paull, J. R. A.; Lewis, G. R.; Tachedjian, G., Structure Activity Relationship of Dendrimer Microbicides with Dual Action Antiviral Activity. *PLoS ONE* **2010**, 5 e12309.
105. Jiang, Y. H.; Emau, P.; Cairns, J. S.; Flanary, L.; Morton, W. R.; McCarthy, T. D.; Tsai, C. C., SPL7013 Gel as a Topical Microbicide for Prevention of Vaginal Transmission of SHIV-(89.6P) in Macaques. *AIDS Res. Hum. RetroViruses* **2005**, 21, 207-213.
106. Moscicki, A.-B.; Kaul, R.; Ma, Y.; Scott, M. E.; Daud, I. I.; Bukusi, E. A.; Shiboski, S.; Rebbapragada, A.; Huibner, S.; Cohen, C. R., Measurement of Mucosal Biomarkers in a Phase 1 Trial of Intravaginal 3% StarPharma LTD 7013 Gel (VivaGel) to Assess Expanded Safety. *Acquir. Immune Defic. Syndr.* **2012**, 59, 134-140.

107. O'Loughlin, J.; Millwood, I. Y.; McDonald, H. M.; Price, C. F.; Kaldor, J. M.; Paull, J. R. A., Safety, tolerability, and pharmacokinetics of SPL7013 gel (VivaGel): a dose ranging, phase I study *Sex. Transm. Dis.* **2010**, *37*, 100-104.
108. StarPharma, <https://starpharma.com/news/328>. [Accessed January 2021].
109. Mahmudpour, M.; Roozbeh, J.; Keshavarz, M.; Farrokhi, S.; Nabipour, I., COVID-19 cytokine storm: The anger of inflammation. *Cytokine* **2020**, *133*, 155151.
110. Lagarce, F., Nanomedicines: promises and reality. *Drug Discov. Today* **2020**, *25*, 473-474.
111. Guidolin, K.; Zheng, G., Nanomedicines lost in translation. *ACSNano* **2019**, *13*, 13620-13626.
112. Cheng, Z.; Al Zaki, A.; Hui, J. Z.; Muzykantov, V. R.; Tsourkas, A., Multifunctional nanoparticles: cost versus benefit of adding targeting and imaging capabilities. *Science* **2012**, *338*, 903-910.
113. Wua, L.-P.; Wang, D.; Lic, Z., Grand challenges in nanomedicine. *Mater. Sci. Eng. C* **2020**, *106*, 110302.
114. Huynh, E.; Zheng, G., Engineering Multifunctional Nanoparticles: All-in-One Versus One-for-All. *Wiley Interdiscip. Rev. Nanomed Nanobiotechnol.* **2013**, *5*, 250-265.
115. Pérez, J.; Bax, L.; Escolano, C., Roadmap Report on Dendrimers. http://phantomsnet.net/files/NRM_Dendrimers_final.pdf **2005**.
116. Mignani, S.; El Kazzouli, S.; Bousmina, M. M.; Majoral, J.-P., Dendrimer space concept for innovative nanomedicine: a futuristic vision for medicinal chemistry. *Prog. Polym. Sci.* **2013**, *38*, 993-1008.
117. Venditto, V. J.; Szoka, F. C., Cancer nanomedicines: So many papers and so few drugs! . *Adv. Drug Delivery Rev.* **2013**, *65*, 80-88.
118. Swenson, S., The dendrimer paradox - high medical expectations but poor clinical translation. *Chem. Soc. Rev.* **2015**, *21*, 4131-4144.
119. Sanhai, W. R.; Sakamoto, J. H.; Canady, R.; Ferrari, M., Seven challenges for nanomedicine. *Nature nanotechnology* **2008**, *3*, 242-244.
120. Mignani, S.; Shi, X.; Rodrigues, J.; Roy, R.; Muñoz-Fernández, A.; Ceña, V.; Majoral, J.-P., Dendrimers toward Translational Nanotherapeutics: Concise Key Step Analysis. *Bioconjugate Chem.* **2020**, *31*, 2060-2071.
121. Killups, K. L.; Campos, L. M.; Hawker, C. J., Robust, Efficient, and Orthogonal Synthesis of Dendrimers via Thiol-ene "Click" Chemistry. *J. Am. Chem. Soc.* **2008**, *130*, 5062-5064.
122. Thomas, O.; Lagarce, F., Lipid Nanocapsules: A Nanocarrier Suitable for Scale-Up Process. *J. Drug Deliv. Sci. Technol.* **2013**, *23*, 555-559.
123. Sengupta, S., Clinical translational challenges in nanomedicine. *MRS Bulletin: Organic Nanoparticles for Drug Delivery and Imaging* **2014**, *39*, 259 - 264.
124. Majoral, J.-P.; Shi, X.; Mignani, S., New opportunities of dendrimers for theranostic approaches to personalized medicine. *Science China Materials, Springer* **2018**, *61*, 1365-1366.
125. Cunningham, S., 3 tips for pharma startup success. *Drug Discov. Today* **2020**, *25*, 1291-1292.
126. Triggie, D. J., The chemist a astronaut: searching for biologically usefull space in the chemical universe. *Biochem. Pharm.* **2009**, *78*, 217-223.
127. Arvinas, <https://docplayer.net/39418925-Targeted-protein-degradation-of-pathological-proteins.html>. [Accessed December 2020].
128. Ottl, J.; Leder, L.; Schaefer, J. V.; Dumelin, C. E., Encoded library technologies as integrated lead finding platforms for drug discovery. *Molecules* **2019**, *24*, 1629.
129. Mignani, S.; Shi, X.; Steinmetz, A.; Majoral, J.-P., Multivalent Copper(II)-Conjugated Phosphorus Dendrimers with Noteworthy In Vitro and In Vivo Antitumor Activities: A Concise Overview. *Mol. Pharmaceutics* **2020**, <https://dx.doi.org/10.1021/acs.molpharmaceut.0c00892>.

130. Mignani, S.; El Brahmī, N.; Eloy, L.; Poupon, J.; Nicolas, V.; Steinmetz, A.; El Kazzouli, S.; Bousmina, M. M.; Blanchard-Desce, M.; Caminade, A.-M.; Majoral, J.-P.; Cresteil, T., Anticancer copper(II) phosphorus dendrimers are potent proapoptotic Bax activators. *Eur. J. Med. Chem.* **2017**, *132*, 142e156.
131. Fan, Y.; Lin, L.; Yinc, F.; Zhua, Y.; Shena, M.; Wang, H.; Dub, L.; Mignani, S.; Majoral, J.-P.; Shi, X., Phosphorus dendrimer-based copper(II) complexes enable ultrasound-enhanced tumor theranostics. *Nano Today* **2020**, *33*, 100899.