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Clinical diagonal translation of nanoparticles: case studies in dendrimer nanomedicine

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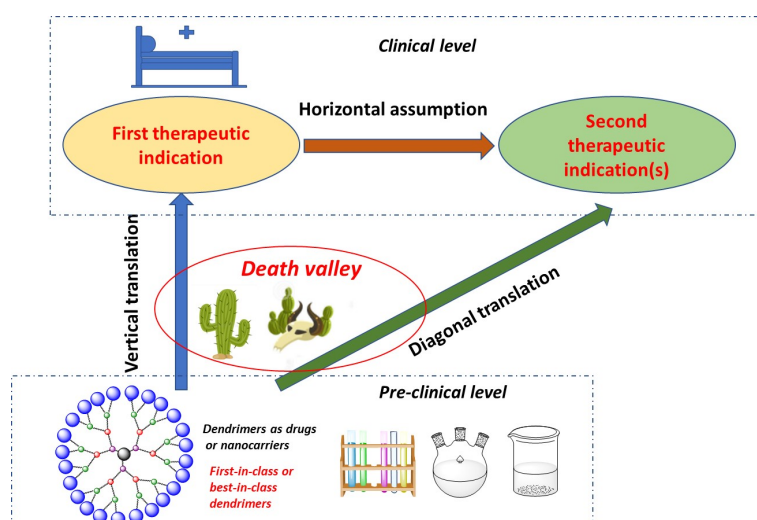
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TOC



Keywords :

Nanomedicine, dendrimers, first-in-class nanodrugs, best-in-class nanodrugs, vertical and diagonal translations, clinical multifunctionality

Highlights :

- Rapidly growing interest in nanotechnology for medical applications
- First-in-class and best-in-class dendrimers in nanomedicine
- Clinical multifunctionality of dendrimers, and other nanoparticles
- Vertical and diagonal translation principles for dendrimers, and other nanoparticles

Abstract:

Among the numerous nanomedicine formulations, dendrimers have emerged as original, efficient, carefully assembled, hyperbranched, polymeric nanoparticles based on synthetic monomers. Dendrimers are used either as nanocarriers of drugs or as drugs themselves. When used as drug carriers, dendrimers are considered '*best-in-class agents*', modifying and enhancing the pharmacokinetic and pharmacodynamic properties of the active entities encapsulated or conjugated with the dendrimers. When used as drugs themselves, dendrimers represent a novel category of "first-in-class" drugs. The purpose of this original review is to analyse the different strategies involved in the development, application, and impact of dendrimers as drugs. We examine a selection of nanoparticles that use multifunctional elements and demonstrate clinical multifunctionality, and we extend these principles to applications in dendrimer nanomedicine design. Finally, for practical consideration, the concepts of vertical and diagonal translation are introduced as potential strategies to facilitate dendrimer development.

Introduction

Nanotechnology has made a significant impact on the delivery of drugs, as well as through their development as drugs themselves.¹ A broad range of nanoformulated products have been approved by the United States Food and Drug Administration (US FDA) and European Medicines Agency (EMA), including liposomal formulations (e.g., Abelect®, AmBisome®, Amphotec®), PEGylated liposomes (e.g., DauxoXome®, Doxil®), nanocrystal formulations (Emend, Megace ES®, Rapamune®, Tricor®, Triplide®), nanoparticle formulations, (e.g., Abraxane®, Estrasorb®), and dendrimers (e.g., Vivagel®).

Nanodelivery platforms (e.g., Doxil®, DauxoXome®, Abraxane®) can improve the solubility, bioavailability and pharmacokinetic/pharmacodynamic (PK/PD) profile of the drug and reduce off-target effects of the encapsulated/complexed therapeutic agents. The current renewed interest in nanomedicines is due in part to their involvement in several of the vaccines against SARS-CoV-2. The vaccines developed by BioNTech-Pfizer (BNT 162b2) and Moderna (mRNA-1273) are based on liposomal nanoparticles encapsulating strands of mRNA encoding the SARS-CoV-2 spike protein.²

Among the numerous nanoformulations including dendritic polymers such as polydisperse frameworks (e.g., comb polymers, star polymers, hyperbranched polymers, reticulated polymers, and dendrigrafts), monodispersed framework dendrimers have emerged as novel, efficient, carefully-assembled, hyperbranched polymeric nanoparticles based on synthetic monomers.³ To date, there are over 100 families of dendrimers⁴, including poly(amidoamine) (PAMAM) dendrimers,⁵ poly(propyleneimine) (PPI) dendrimers,⁶ phosphorous dendrimers,⁷ carbosilane dendrimers,⁸ poly(L-lysine) (PLL) dendrimers,⁹ and poly(ester-amide)¹⁰ dendrimers. The size of these spheroid or globular tree-like structures is tightly regulated, and their surface is highly customisable by the introduction of various chemical groups. The major architectural elements are the inner core as a focal point, interior branching, internal cavities in the periphery, and the terminal groups. Figure 1 shows also a well-known G4 PAMAM dendrimer.

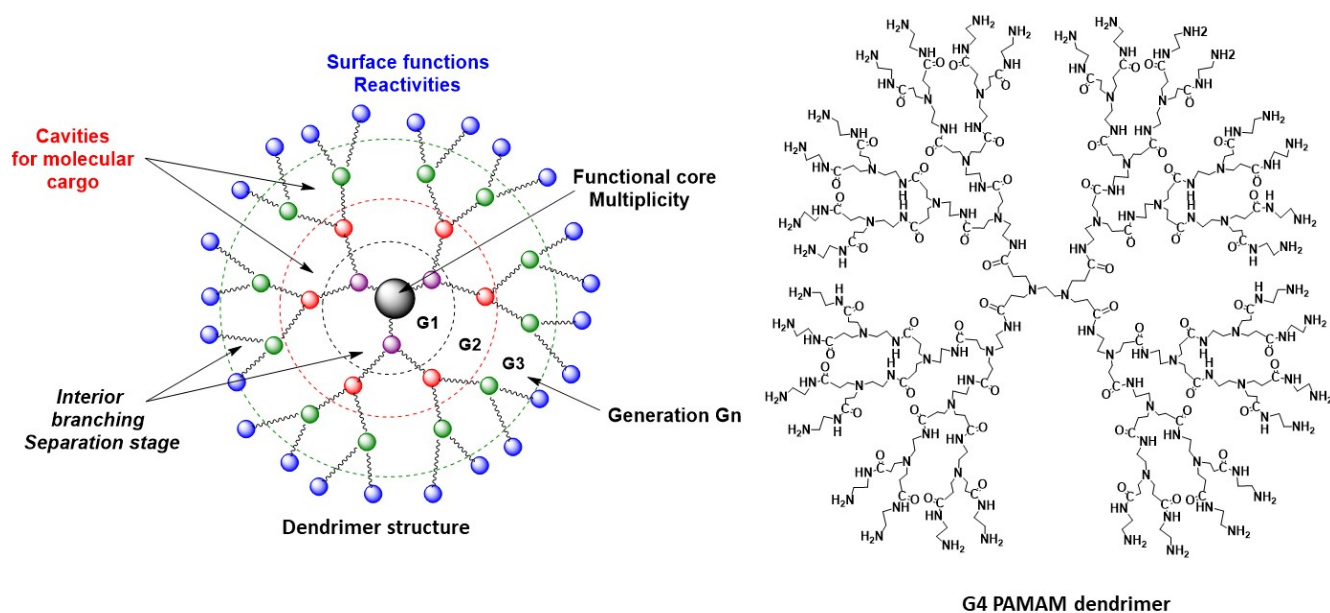


Figure 1. 2D schematic structure of dendrimer and chemical structure of G4 PAMAM dendrimer.

Dendrimers can be classified by generation number (e.g., G0-Gn), according to their symmetric repetition of branches (Figure 1). Size and spherical shape of dendrimers can be precisely controlled by the chemical composition and generation (Gn) of the repetitive units, as well the number of surface groups, which increases geometrically with the generation. Importantly, void spaces enable the encapsulation of biologically active compounds like small molecules, macromolecules, peptides, and metal nanoparticles. Additionally, conjugation or complexation of components such as small molecules, macromolecules, targeting peptides, antibodies, and nucleic acids with the surface groups has been explored. In these cases, dendrimer nanoformulations are developed as nanocarriers. Another area of research is the development of dendrimers with inherent activity; however, few such examples have been described to date. Though not particularly productive in itself, this represents a novel strategy for finding and developing new drugs.

Interestingly, Tomalia and colleagues defined the concept of nanoperiodic road map based on hard and soft nanoscale building blocks with the following characteristics: 1) size; 2) shape; 3) surface chemistry; 4) flexibility/rigidity; and 5) elemental composition and architecture.¹¹ As a general trend, higher-generation polycationic dendrimers have shown cytotoxicity and hemolysis effects.¹² On the other hand, polyanionic dendrimers (e.g. carboxylated, sulfonated, phosphonated dendrimers, and neutral dendrimers bearing poly(ethylene oxide) PEG chains and acetyl, carboxyl, mannose and galactose end groups, exhibited less toxicity versus polycationic dendrimers. Low polydispersity and biocompatibility are the two main challenges to be considered for the use of dendrimers in nanomedicine as nanocarriers and as drugs (active *per se*).^{13,3} An interesting study was performed by Ciolkowski and colleagues concerning the cytotoxicity of PAMAM dendrimers relating their surface polarity.¹⁴ Several reviews highlight the *in vitro* and *in vivo* biocompatibility profiles of dendrimers.^{15,16} The precise chemical control of the dendrimer architecture controls the high drug elimination half-life, linked to the long blood circulation half-life, and the appropriate rate of release of the drug.³ An outstanding analysis of the *in vivo* biocompatibility of nanoparticles in general and dendrimers in particular has been performed by Khandare and Haag et al.¹⁷

As an interesting example, Zhang et al. highlighted a systematic analysis of the cellular uptake, intracellular transportation, and efflux of G4 PAMAM-

NH₂ dendrimers in MCF-7/ADR multidrug-resistant breast cancer cells, using MCF-7 cells sensitive breast cancer cells as the control.¹⁸ The uptake rate of G4 PAMAM-NH₂ was lower in breast cancer MCF-7/ADR cell lines than in MCF-7 cells, whereas its exocytosis was greater in MCF-7/ADR cells versus in MCF-7 cells. The two main reasons for these observations are as follows: 1) the elimination of G4 PAMAM-NH₂ from P-glycoprotein; and 2) the multidrug resistance-associated protein in MCF-7/ADR cells. The micropinocytosis process (also called “cell drinking”) – a type of endocytosis involving the nonspecific uptake of extracellular material – played a more important role in its uptake in MCF-7/ADR cells than in MCF-7 cells. The endoplasmic reticulum and Golgi complex are the major participants in the exocytosis process. Another interesting example was described by Oddone et al. This team demonstrated that G4-PAMAM dendrimers, conjugated with fluorescein isothiocyanate (FITC) as imaging agent, in human myometrial cells, is taken up by clathrin-mediated endocytosis with endosomal and lysosomal localization.¹⁹ In 2018, Chowdhury and colleagues, showed that methylprednisolone-loaded carboxymethylchitosan/G1.5 PAMAM dendrimer are taken up by endocytosis into astrocytes, increasing in the frequency of transient exocytotic fusion.²⁰ In addition, based on co-localization imaging studies, the clearance process of dendrimers through exocytotic vesicles is time dependent.

Both non-targeted and targeted drug delivery strategies have been used with the dendrimer nanoplateforms. In the oncology domain (the most explored therapeutic application), the targeting approach takes advantage of the attachment of specific groups (e.g. folic acid, RGD peptide, avidin–biotin moiety, glycopeptide- β -galactoside, riboflavin, lactoferrin, transferrin and Tamoxifen) on the surface of dendrimers to preferentially target cancer cell lines versus normal cell lines increasing the specificity.²¹ The groups on the surface of these functionalized dendrimers specifically interact with over-expressed receptor targets on the surface of tumours, allowing the preferential accumulation of the carried-drug in the tumour.

In this review, we analyse the most relevant strategies for the development, application, and impact of dendrimers as drugs within the nanomedicine domain. Our analysis is based on an understanding of the principles of multifunctionality and clinical multifunctionality as applied to a selection of nanomedicines in general and extended to dendrimers. For practical consideration, the concepts of vertical and diagonal translation are also

introduced in the potential pathway that a dendrimer might take from the laboratory to the clinic. The first section will analyze the general aspects of first-in-class and best-in-class drug strategies in pharmaceutical industries to develop new drugs. The second section will investigate first-in-class and best-in-class strategies to develop new dendrimers as nanocarriers and as drugs themselves. The third section will present selected examples of nanoscale multifunctionality and clinical multifunctionality in nanomedicine of nanoparticles opening new therapeutic applications for dendrimers. Vertical, horizontal, and diagonal translation pathways for clinical dendrimer development will be highlighted in section four. The last section presents a conclusion and perspectives.

1. First-in-class and best-in-class strategies to develop new drugs in pharmaceutical industries: a brief survey

Modern pharmaceutical companies typically build their R&D pipelines by looking for either first-in-class (FIC) drugs, or best-in-class (BIC) drugs. First-in-class drugs are entirely novel, acting on specific new druggable targets, and typically achieve a large market share. They tend to do well in situations with a strong, dynamic demand for drugs to treat diseases with unmet needs. These drugs are the main drivers of pharmaceutical innovation and often allow drug companies to obtain a monopoly through intellectual property (patent) protection. Best-in-class drugs on the other hand, belong to an existing therapeutic class, and usually seek to optimize or outperform existing drugs in some fashion. The later entrants in a specific therapeutic domain will need to develop BIC medicines. Interestingly, phenotypic approaches – identification of molecules with the ability to alter, for instance, a cell's phenotype - have been shown to be more successful in finding FIC small molecules, whereas target-based-approaches more often lead to successful development of BIC drugs.

Few comparisons between BIC and FIC drug strategies have been published to date; however, an interesting analysis was performed by Schulze and Ringel regarding the therapeutic advantages and commercial successes, within therapeutic indications related to drugs launch order (first, second, third, or fourth).²² Clearly, given the higher therapeutic advantages, the first-in-class entering the market drugs are slightly better than the second drugs (best-in-class) entering the market, and strongly better than the drugs entering the market third. Best-in-class drugs which entered the market two to five years, and more than five years after FIC, have only 38% and 17% of the value of

therapeutic advantages compared to others in same class, respectively. Consequently, the authors suggested three potential strategies for consideration in drug development: 1) chance to be first-in-class; 2) rapid best-in-class development within 2 years (to reasonably compete with the FIC competitor); and 3) if the two prior points (1 and 2) were not involved for later entrant drugs, to be in good market place position to exploit criteria such as: a) strong advantages of the considered drugs within unmet therapeutic field; b) alternative repositioning strategy if initial therapy fails; and c) use of effective commercial organization. Table 1 presents the main advantages and disadvantages of FIC versus BIC.

Table 1. Main advantages and disadvantages of FIC versus BIC

Strategy used	Advantages	Disadvantages
First-in-class (FIC)	<ul style="list-style-type: none"> - Innovative and cutting-edge to treat unmet medical needs (unprecedented patient outcomes) - original drugs combating the lack of innovation in pharmaceutical industries - ensure a strong patent position and freedom to operate - high therapeutic advantages - Boost pipelines (blockbuster drugs) 	<ul style="list-style-type: none"> - unavoidable financial risks of development must be considered
Best-in-class (BIC)	<ul style="list-style-type: none"> - ability to use competitors' studies for information, in parallel with clinical trials - existing therapeutic advantages if 2nd on the market - established clinical need, faster track to insurance 	<ul style="list-style-type: none"> - highly competitive environment with existing compounds that are already in clinical trials or even on the market, and which show efficacy in patients - must show an improvement over its competitor(s). To be

	coverage	<p>superior to its competitors in a crowded market</p> <ul style="list-style-type: none"> - low therapeutic advantage if 3rd on the market - steal market share challenging from competitors
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2. First-in-class and best-in-class strategies to develop new dendrimers as nanocarriers and as drugs themselves

Figure 2 depicts the first-in-class and best-in-class dendrimer types. First-in-class corresponds to dendrimers as drug active per se, whereas best-in-class corresponds to dendrimers as nanocarriers improving the therapeutic profile of known drugs-loaded dendrimers.

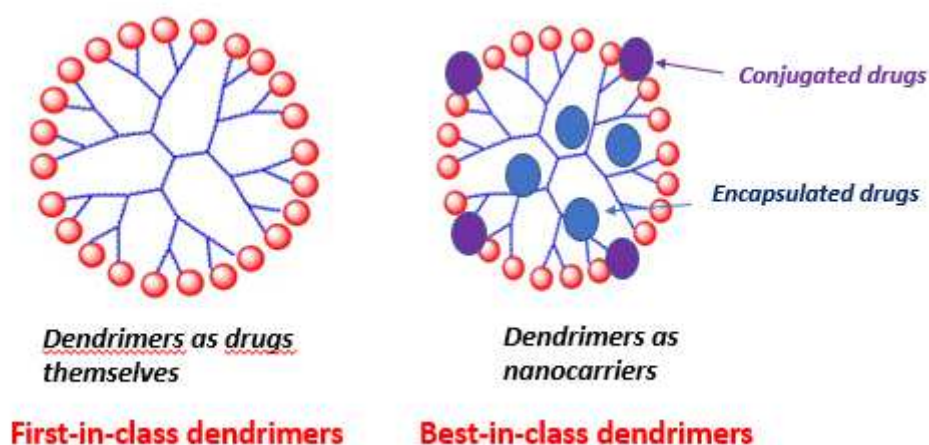


Figure 2. First-in-class and best-in-class dendrimer types

2.1. Barriers to the clinical translation of dendrimers

Despite 40 years of fundamental and pre-clinical research,²³ there has been very little clinical uptake of dendrimer nanomedicines. These translational challenges were analysed in 2013 by Vendito and Szoka, who described the development of nanomedicines versus small molecules and monoclonal antibodies in the oncological domain.²⁴ 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. Based on several reviews, including Swenson,²⁵ Guidolin and Zheng,²⁶ Sanhai,²⁷ and Mignani, Shi, Rodrigues, and Majoral,²⁸ several translational barriers emerged: 1) complex, slow, and costly synthesis; 2) the regulatory need for monodispersity and chemical and biological stability; 3) attractiveness versus other nanocarriers, such as liposomes or polymeric NPs; 4) reproducible scale-up synthesis under good manufacturing practices (GMP) and manufacturing; 5) strong advantages over current treatments to convince regulatory agencies (i.e., the FDA and EMA) to grant market access; and 6) development of biocompatible dendrimers with advantages over "internal competitors" in the pipelines of pharmaceutical companies. These challenges were compounded by a trend towards the development of complex nanomedicines through the addition of multifunctional elements.²⁹ Recently, we analysed the inherent translational problems to be solved during the development of dendrimers (best- and first-in-class) from bench to bedside and proposed tailored solutions.³⁰

2.1. Limitless possibilities for the use of dendrimers as nanocarriers for best-in-class strategy

Many reviews described the use of dendrimers as nano-carriers through various mechanisms, including encapsulation/drug loading, electrostatic complexation, or conjugation.³¹ The majority of these drugs are anticancer agents used for targeted and non-targeted antineoplastic therapy, such as cisplatin, paclitaxel, 5-fluorouracil, camptothecin (CPT), methotrexate and doxorubicin,^{16,21} as well as natural products,^{16,32,33} antisenses,³⁴ aptamers,³⁵ and siRNAs.³⁶ These studies clearly demonstrate the usefulness of dendrimers that conjugate or encapsulate drugs used to treat various diseases, including cancer, infection, or inflammatory disease, by improving their intrinsic biological activity and decreasing their systemic toxicity.^{21,37,38} This strategy makes it possible to improve the overall efficacy of these drugs through improvements in their PK/PD, facilitating the transition of nanoparticles like dendrimers to become "best-in-class" compounds (as seen in the application of Doxil® and Abraxane®).

Recently, Starpharma Holdings Ltd. (Melbourne, Australia) has increased the range of therapeutic applications of its drugs. They are developing a PEGylated poly-L-lysine dendrimer called DEP® docetaxel as a BIC drug, using

the conjugation of the anticancer agent docetaxel (Taxotere®) to the dendrimer surface. This nanoparticle is in Phase II clinical trials for the treatment of lung and prostate cancer. Based on the BIC strategy, in collaboration with AstraZeneca, Starpharma is developing AZ DEP AZD0466, a PEGylated lysine dendrimer conjugated to AZD4320 (an AstraZeneca Bcl2/xL inhibitor), aiming to treat solid and haematological tumours (blood cancers).³⁹

2.2. Limitless possibilities for the use of first-in-class dendrimers as drugs

Another important direction in nanomedicine is to develop dendrimers as active drugs in their own right, in several therapeutic areas, including anti-Alzheimers,^{40,41} anticancer,²¹ anti-viral,⁴² anti-microbial,^{43,44} anti-prion.⁴⁵ Importantly, immuno-active dendrimers⁴⁶ were developed including 1) glycodendrimers activating T helper type 1 (Th1) cells and enhancing natural killer (NK) cell activity;⁴⁷ 2) aza-bisphosphonate (ABP)-capped phosphorous dendrimers, first developed by Majoral et al., inhibiting IL-2-driven CD4+ T cell expansion and inducing NK cell proliferation after the interaction with monocytes;⁴⁸ and 3) pyrrolidone (Pyr)-modified poly(amidoamine) (PAMAM) dendrimers preventing the stimulation of the NF-κB signaling pathway.⁴⁹

An interesting early analysis has been undertaken by Gajbhiye and Jain et al.⁵⁰ These nanoparticles were developed using the FIC drug development strategy, but few examples were highlighted. Table 2 shows selected first-in-class dendrimers related to their generation, number and nature of active chemical groups on the surface which are key points for the biological activity, therapeutic applications, and impact status. Mintzer, Grinstaff et al. arguably presented the role of dendrimer multivalency to combat emerging and re-emerging infectious diseases.⁵¹ Recently, Ortega et al. advocated the use of dendrimers and dendritic materials against several viral infections including Enterovirus A71, Ebola virus, Zika virus, and Dengue virus.⁵²

Importantly, the pharmaceutical company Starpharma Holdings Ltd. succeeded in introducing dendrimers, as first-in-class nanoparticles, in clinical trials. This company introduced the polylysine-based dendrimer SPL7013 (Vivagel®), which demonstrated statistically significant efficacy in treating bacterial vaginosis in pivotal multi-centre Phase III trials. VivaGel® bears 32 sodium 1-(carboxymethoxy)naphthalene-3,6-disulfonate surface groups. Very recently, Starpharma announced the development of VivaGel® as a potent

antiviral agent against the respiratory syncytial virus (RSV), for use both before and after exposure to the virus, using nasal spray technology (VIRALEZE™).³⁹

2.3. Evolution of the model-based drug development (MBDD) as a rational approach to dendrimer development

Inspired by an article by Milligan et al.,⁵³ Figure 3 presents the evolution of the model-based drug development (MBDD) as a rational approach to accelerate drug application, including the development of NPs such as dendrimers as nanocarriers or drugs related to BIC *versus* FIC, and their respective strategy of development of target-based approach over phenotypic screening.

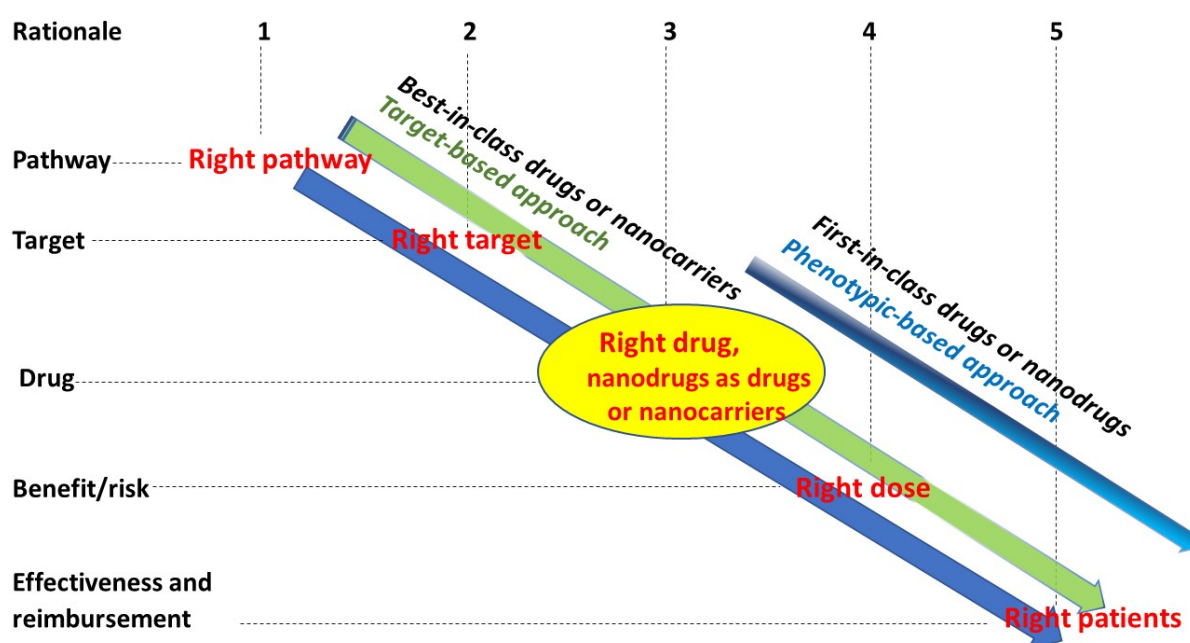


Figure 3. Evolution of MBDD as a continuum of learn-confirm-predict at each decision point of drug development, including the development of NPs such as dendrimers as nanocarriers or drugs related to best-in-class *versus* first-in-class

3. Case studies in nanoscale multifunctionality and clinical multifunctionality of nanoparticles: a new hope for dendrimers

Recently, Guidolin and Zheng,²⁶ proposed the term “*clinical multifunctionality*” to describe the capacity of a single nanomedicine to confer multiple diagnostic or therapeutic advantages, in contrast to traditional

“nanoscale multifunctionality”.⁵⁴ Table 3 presents a non-exhaustive list of NPs⁵⁵ and their corresponding degree of clinical and nanoscale multifunctionality⁵⁶. Agents that are not clinically multifunctional (“N” in Table 3) are suitable only for a single clinical application, while those that possess clinical multifunctionality (“Y” in Table 3) may be applied to solve several different clinical problems. The distinction that Guidolin and Zheng make with the proposal of these terms is that some NPs may possess many nanoscale multifunctional elements (thereby being multifunctional at the nanoscale) but that these translate into only a single clinical application, whereas other NPs may possess a relatively simple nanoscale design with a single functional element, but this single functional element may be capable of solving multiple clinical problems (clinical multifunctionality) on the application scale.

Table 3. Multifunctionality and clinical multifunctionality of a selection of NPs including dendrimers

Strategy of development	Multifunctionality	Clinical multifunctionality	Examples of nanomedicines in the clinic to tackle cancers and infections
Best-in-class	N	N	Marquibo®, Onivyde®, Doxil®, Myocet®, Caelyx®, Myocet®, Eligard®, Smancs®, Ontak®, mRNA-1273, BNT 162b2
	N	Y	Abraxame®, FeraMax®, Megace® ES, Exparel®, Guanabenz®, DEP® docetaxel (dendrimers as nanocarriers) , AZ DEP AZD0466 (dendrimers as nanocarriers)
	Y	N	Vyxeos®, ⁶⁴ Cu-MM-302
	Y	Y	-
First-in-class	N	N	Oncaspar®, Prothecan®, Dendrimers active per se (no example)
	N	Y	VivaGel®* (dendrimers active per se)

*based on preclinical studies as antiviral agent (see text)

Within the BIC strategy of development, neither clinical multifunctionality nor nanoscale multifunctionality were observed for: 1) Doxil®, a PEGylated liposomal doxorubicin which was the first NP approved by the FDA in 1995⁵⁷, 2) Myocet®, a non-PEGylated liposomal doxorubicin for the treatment of metastatic breast cancer^{58,59} (EMA approval: 2000), 3) Marquibo®, a non-PEGylated cholesterol liposomal NP encapsulating the anti-cancer agent vincristine, improving the PK/PD⁶⁰ (FDA approval: 2012), 4) Eligard®, an acetate leuprolide nanoparticle based on a nanopeptide NP comprised of a combination of biodegradable polymers in a liquid carrier, for the hormonal

treatment of prostate cancer. Acetate leuprolide binds to and activates gonadotropin-releasing hormone (GnRH) receptors,⁶¹ 5) Onivyde®, a PEGylated liposomal formulation of irinotecan, used against metastatic pancreatic adenocarcinoma,⁶² 6) PEGylated liposomal doxorubicin (Caelyx®), which is safe and moderately effective in patients with recurrent high-grade III glioma, administered alone or in combination with tamoxifen,⁶³ 7) Smancs®, a conjugate of neocarzinostatin and poly(styrene-comaleic acid) for treating primary unresectable hepatoma,⁶⁴ and 8) Onivyde®, a PEGylated liposomal irinotecan used against metastatic pancreatic cancer (FDA approval: 2015).⁶⁵

Clinical multifunctionality can be conceptualized as a refocussing of the major therapeutic indication of the nanomedicine. Take the case of Abraxane® for example; albumin-bound paclitaxel intended to be the first Cremophor®-free anticancer agent. The initial therapeutic role that Abraxane® sought to fill was to avoid the side effects of Cremophor® (severe anaphylaxis and prolonged sensory neuropathy).⁶⁶ Despite these original intentions, the complexation of paclitaxel to endogenous albumin was found to improve the delivery of paclitaxel to tumours through enhanced transport across endothelial cells, which consequently delivered a higher dose of paclitaxel. Abraxane® is used to treat breast cancer after the failure of combination chemotherapy for metastatic disease and is a first-line treatment for locally advanced or metastatic non-small cell lung cancer (in combination with carboplatin). In addition, Abraxane® is indicated for the first-line treatment of patients with metastatic pancreatic adenocarcinoma (in combination with gemcitabine).⁶⁷ In addition to these direct therapeutic advantages, Abraxane® also achieved its original goal, circumventing the common hypersensitivity reactions seen following the administration of many chemotherapeutics, and thereby obviating the need for pre- or post-medication (with antihistamines, corticosteroids, and bronchodilators, etc.). This is an excellent example of a nanomedicine with a simple nanoscale design (not multifunctional at the nanoscale) that achieved clinical success because of its clinical multifunctionality. Such clinical successes make liposomes and albumin-based nanoparticles especially attractive platforms for nanomedicine development.

Another interesting example of a clinically multifunctional NP is FeraMax®, a carbohydrate-coated superparamagnetic iron oxide NP (SPIO), originally marketed for the treatment of iron deficiency anaemia. In addition to this primary therapeutic indication, FeraMax® can be used as a contrast agent for magnetic resonance imaging of focal hepatic lesions, though this has not seen much clinical uptake.⁶⁸ Interestingly, Exparel®, a liposomal bupivacaine NP with extended duration of action, was originally developed as a local

anaesthetic for use following bunionectomy and haemorrhoidectomy, but which has been investigated for numerous applications in postoperative pain management.⁶⁹ While some might argue that this is essentially the same clinical application (i.e., local anaesthesia), the expansion to use in a wider range of clinical scenarios (e.g., orthopedic surgery) drastically improves the market for these drugs. Following the same strategy, DEP[®] docetaxel used a dendrimer as a nano-carrier to treat a wide range of clinically important tumour types. Consequently, these drugs achieve clinical multifunctionality without the use of a multifunctional design on the nanoscale, thereby saving time and money in the pre-clinical stages and simplifying regulatory approval and scale-up for clinical application.

In some situations, however, multifunctional nanoscale design facilitates clinical multifunctionality. This concept is what gave rise to the burgeoning field of theranostics.⁷⁰ The development of a highly PEGylated liposome MM-DX-929, entrapping a combination of a positron emission tomography (PET) agent ⁶⁴Cu (copper-64) and 4-DEAP-ATSC chelator for tumour deposition and patient selection was highlighted.⁷¹ Based on this principle, the design of PEGylated liposomal doxorubicin encapsulating ⁶⁴Cu (copper-64) chelated with 4-DEAP-ATSC and an anti-HER2 scFv F5-PEG-DSPE immunoconjugate, named ⁶⁴Cu-MM-302, showed high tumour deposition for theranostic purposes.⁷² Treatment in 19 patients with metastatic breast cancer, plus trastuzumab with and without cyclophosphamide, provided high nanoparticle deposition in tumours. This technique represents a powerful strategy to identify patients with HER-2 positive breast cancer, as well for therapeutic purposes.⁷³

Currently, several FIC PEGylated proteins are used in the clinical treatment of cancer, including: 1) PEG-L-asparaginase Oncaspar[®] for the treatment of acute lymphoblastic leukaemia,⁷⁴ and 2) PEG-camptothecin (Prothecan[®]), an ester-based prodrug.⁷⁵ These therapeutic agents are unifunctional on both the nano- and clinical scale. Interestingly, the polylysine-based-dendrimer SPL7013 (Vivagel[®]) demonstrated significant efficacy in pivotal Phase III trials to treat bacterial vaginosis. Vivagel[®] is used for the treatment and prevention of bacterial vaginosis (BV), as well the prevention of sexually transmitted infections (STIs).⁷⁶ In 2018, Starpharma announced the development of SPL7013 for the treatment and prevention of microbial infections of the eye, such as conjunctivitis.³⁹ Very recently, Starpharma announced **also** the preclinical development of SPL7013 as a potent antiviral agent against respiratory syncytial virus (RSV) before and/or after exposure, using nasal spray technology (VIRALEZE). Expanding studies to other respiratory viruses, including SARS-CoV-2 (the coronavirus that causes COVID-19) and

influenza, are ongoing.³⁹ SPL7013 has been shown to be viricidal, inactivating >99.9% of SARS-CoV-2 within one minute.⁷⁷ For this reason, Vivagel® is classed as clinically multifunctional. In Table 3, we envisaged that FIC dendrimers, like those found in Table 2, may achieve clinical multifunctionality without the addition of nanoscale multifunctional elements.

Unlike other NPs, which are generally developed for intravenous (IV) administration, dendrimers represent an useful nanoplatform, for exploring delivery via enteral (oral) and topical (transdermal, ocular, or transmucosal) routes of administration in addition to standard intravenous administration.⁷⁸ An outstanding example is Vivagel®, where topical and nasal administration is used to treat two different disease types.

Recently, Orpheris, Inc. (USA) is developing in double-blind Phase II, the dendrimer *N*-acetylcysteine OP-101 in patients with severe COVID-19, reducing the burst inflammatory cytokine storm. The chemical structure is not disclosed.⁷⁹

Many biomedical researchers hope to one day design and market a clinically useful compound and ultimately affect a positive change in the lives of patients and society at large. Despite the large amount of research carried out over recent decades, few NPs (especially dendrimers) have achieved the milestone of entering the clinic. As a general trend, during drug development, the crucial step is to successfully cross the “Valley of Death” between pre-clinical studies based on basic scientific research and clinic application. Recently, the economic aspects for the valuation of biotech companies were analysed by Truebel and Thurston from Bayer.⁸⁰

4. Vertical, horizontal, and diagonal translation for clinical dendrimers development

A significant gap exists between the academic world and industry with respect to knowledge and the scientists that produce it.⁸¹ Seyhan identified and analyzed obstacles to translation, especially for well-developed drugs.⁸² The rate of success in translational science is less than 1%.⁸³ In the dendrimer realm for best- and first-in-class nanoparticles, we suggested tailored solutions to solve the inherent problems in the pathway from bench to bedside.³⁰ Figure 4 presents vertical translation for the development of dendrimers. The horizontal adoption can eventually be achieved, starting from the initial therapeutic application(s) and moving towards further tailored one(s), with the ultimate

result being the diagonal translation of the dendrimer. Based on expansion of clinical indications through off-label use by clinicians, the concept of drug repositioning from 'old' drugs to treat both common and rare diseases represent an attractive and powerful strategy (horizontal adoption, Figure 4).

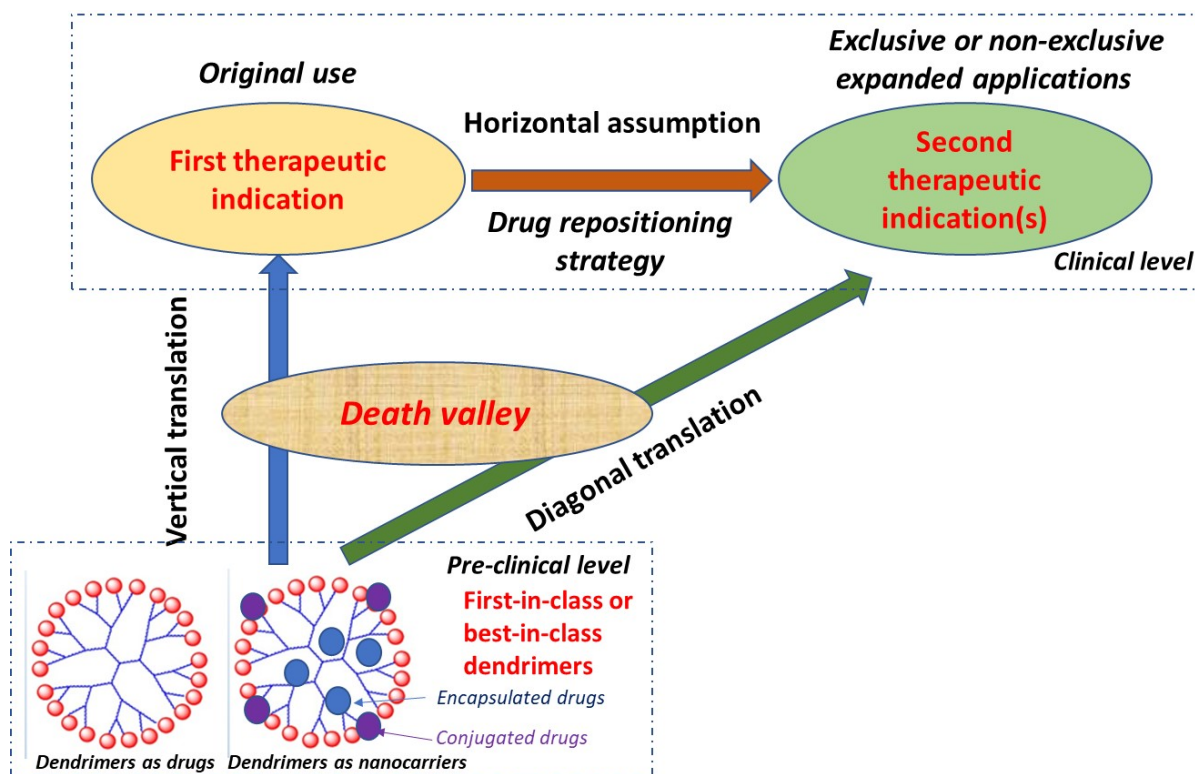


Figure 4. Vertical and diagonal translation principles

As shown in Figure 5, the main advantages of the repositioning strategy over generics and new chemical entities (NCEs) are as follows: 1) lower overall development costs for Phase II and Phase III clinical trials (~US \$300 million versus ~US \$2 billion for a new chemical entity); 2) shorter conventional development timelines (~3–5 years versus 7–10 years), traditional drug development: preclinical studies – Phase 1 – Phase 2ab – Phase 3 – market – Phase 4 versus drug repositioning: Phase 2b – Phase 3 – market – Phase 4; 3) de-risked development compounds (25% from Phase II to market, in contrast to only 10% for conventional drug development); and 4) same potential market, such as similar possibility to achieve blockbuster status versus *de novo*-derived drugs.^{84,85} The COVID-19 pandemic poses a considerable challenge to find effective therapeutic approaches. Repositioning of the drug strategy for COVID-19 has been strongly influenced by strategies from other fields, including as cancer drugs,⁸⁶ anti-HCV, (Human Coronavirus) nucleotide inhibitors⁸⁷ as well using virtual screening strategies for protease inhibitor collection.⁸⁸

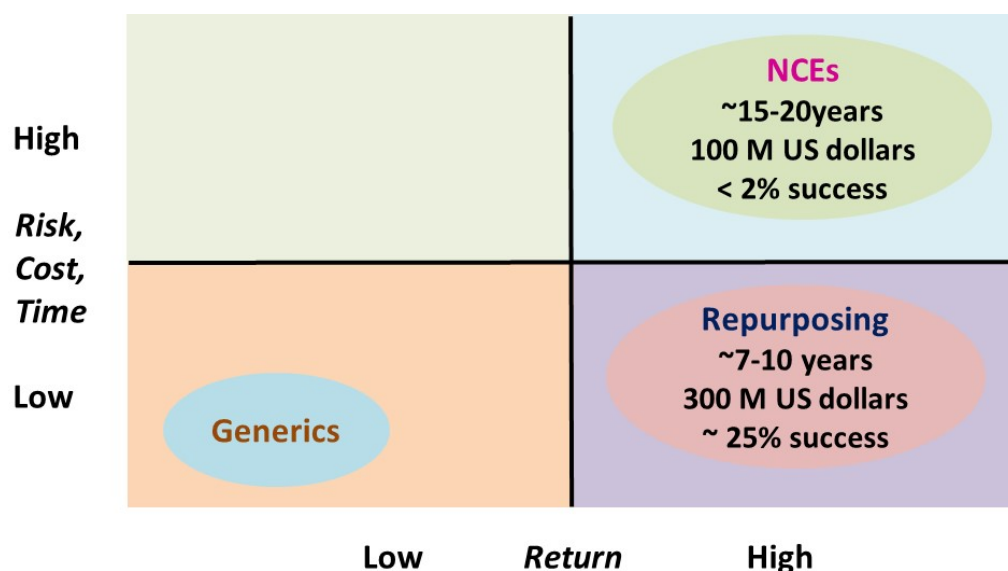


Figure 5. Risk, cost and time versus return on investment for generic, repositioning and classical strategies. NCEs: new chemical entities.

Importantly, repositioning of drugs has also been approached in the nanomedicine realm. Guanabenz® conjugated to gold and silver NPs is approved for use in hypertension and crosses the blood-brain barrier. Medications for the treatment of granulomatous amoebic encephalitis and primary amoebic meningoencephalitis caused by *Acanthamoeba castellanii* and *Naegleria fowleri*, respectively, remain in high demand. Anwar et al. showed that Guanabenz® displayed significant anti-amoebic activity against both *A. castellanii* and *N. fowleri*.⁸⁹

All of the selected FIC dendrimers in Table 1 could potentially be developed according to the strategies indicated in Figure 3. All of these FIC dendrimers are in pre-clinical trials, except for Vivagel®, which has passed through the various clinical phases. Vivagel's manufacturer, Starpharma Holdings, Ltd. is a highly dynamic company that develops platforms based on biocompatible dendrimeric structures, using its know-how and expertise based on the success of Vivagel® as a microbicide for the prevention of HIV, HSV and microbial infections of the eye, and recently for protection against COVID-19 before and/or after exposure to SARS-CoV-2, using nasal spray technology (VIRALEZE).³⁹ This example clearly shows that there is great long-standing interest in the development of dendrimers in nanomedicine, opening doors to the expansion of new applications using multiple delivery routes. Another interesting repositioning strategy is the expansion of the first therapeutic indication of a small molecule to a second one by using nanotechnology to improve the PK/PD of the free drug. For example, Nelfinavir has been FDA

approved as an antiretroviral drug for the treatment of human immunodeficiency virus type 1 (HIV-1) infection. This drug also showed anticancer activity by stimulating apoptosis, but requires a higher dose, which leads to toxicity and therefore limits potential clinical translation. Interestingly, biodegradable poly(lactic-co-glycolic acid) (PLGA) NPs of nelfinavir showed significant efficacy in the treatment of non-small cell lung cancer (NSCLC) by inducing apoptosis and improving tumour penetration.⁹⁰ All of the examples described in Table 1 with N to Y, including both BIC and FIC drugs, can be considered to follow the repositioning strategy.

Diagonal translation, as coined by Guidolin and Zheng,²⁶ refers to the net movement of a drug with respect to its clinical application. To use the example of superparamagnetic iron oxide nanoparticles (SPIONs) as discussed earlier (like Ferumoxytol), these NPs were initially developed, approved, and marketed as therapeutics for the management of iron-deficiency anaemia (“vertically translated” from the pre-clinical setting). Subsequently, they were adopted for use as MRI contrast agents, particularly the imaging of lymph nodes⁹¹ or tumours⁹² (horizontal adoption). This resulted in the net translation of these SPIONs from the laboratory into a clinical application for which the SPION was not necessarily intended or tested at the pre-clinical level – a *diagonal translation*. This phenomenon is possible only because physicians are permitted to use drugs “off-label”; for applications other than those for which the drug is approved by the regional regulator (e.g., FDA, EMA, etc.), thereby *horizontally adopting* them for new applications. As a result, this off-label use can be studied in clinical trials with greater ease and at decreased cost and risk. Because the drug in question already has regulatory approval, there are fewer concerns and less uncertainty regarding the drug’s side effect profile, the drug is more readily available and often less expensive than it would be where it not already in production, and there is less risk to stakeholders like the pharmaceutical company, since their market-share can only be expanded by the addition of indications to use the drug.

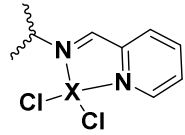
Many drugs, especially NPs, have strong pre-clinical evidence to support seeking regulatory approval for any number of indications; therefore, the decision of which to select is a strategic one. Some might suggest that the most strategic indication to pursue in clinical trials is the one with the greatest potential for benefit, or the one with the strongest pre-clinical evidence; however, a thorough understanding of diagonal translation suggests an alternative strategy that may help drugs like NPs overcome regulatory barriers, particularly those imposed by regulators like the FDA, who require evidence of

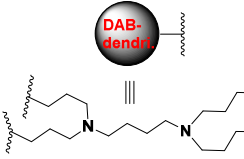
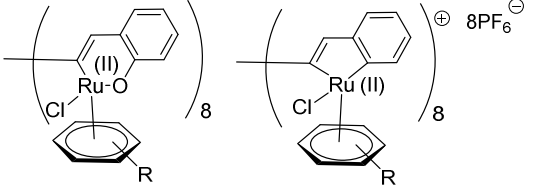
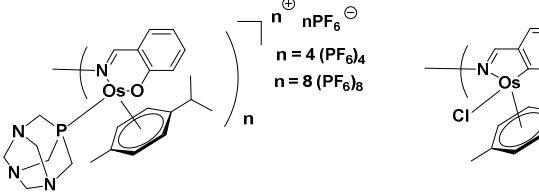
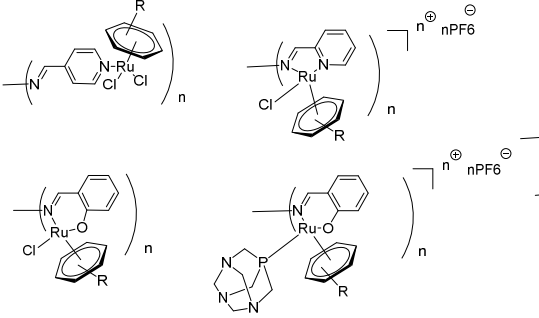
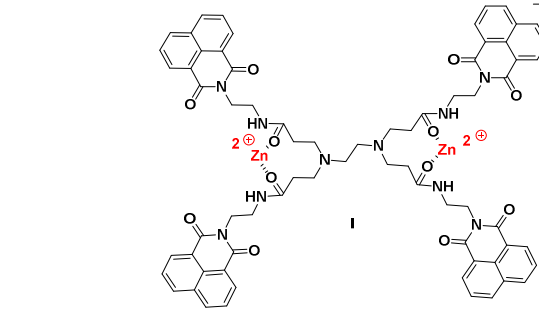
efficacy in addition to evidence of safety. This strategy is to seek regulatory approval for the indication that is the easiest, most economical, or most likely to succeed in clinical trials; essentially this is setting a low bar for success. While this might mean that a drug is initially approved for a less impressive clinical indication, it lowers the regulatory barrier in a safe fashion. Subsequently, the drug can be tested for more clinically important indications both by the pharmaceutical company itself, and by clinicians seeking diagnostic or therapeutic options for patients that have been failed by existing drugs. Examples of horizontal adoption in this manner abound. Whether previous drug-makers have used diagonal translation as a pathway to the clinic intentionally or incidentally is unknown, but they have benefitted from it regardless.

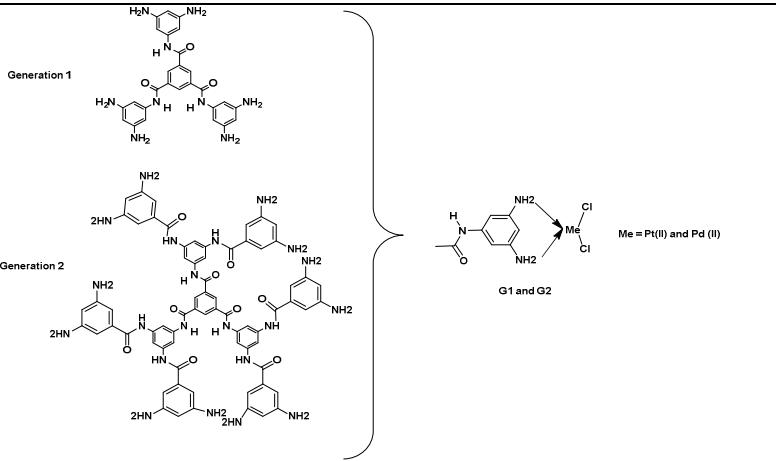
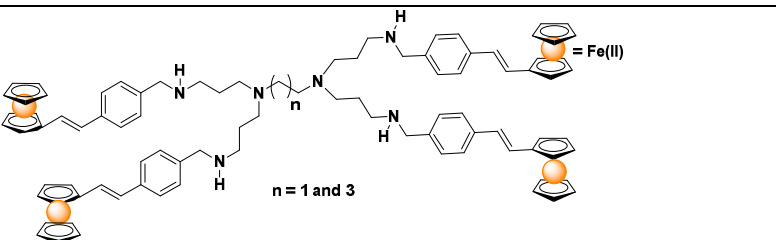
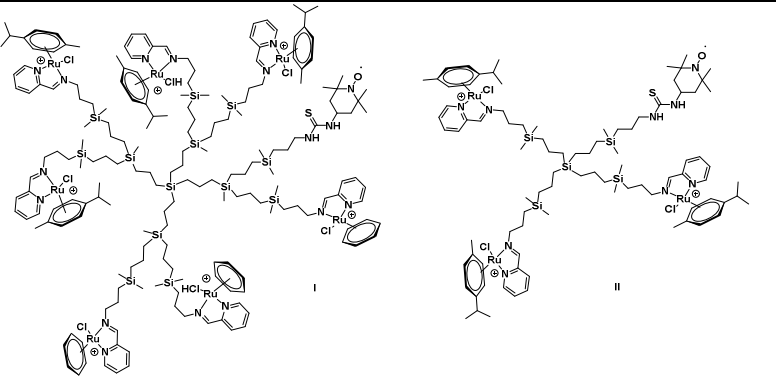
This diagonal translation strategy may be used to introduce to the clinic those drugs which have historically struggled with translation, namely NPs in general, and dendrimers, specifically. Ferumoxytol is an excellent example of a NP that used this diagonal translation pathway. Its initial claimed and approved indication as an iron supplement set an extremely achievable efficacy goal that undoubtedly facilitated its translation. The use of a nanoformulation in this case is likely non-contributory to its efficacy as an iron supplement since more than ten other formulations of iron supplement exist with the clinical differences in efficacy being largely academic in nature; however, once approved, Ferumoxytol was available as an approved drug for exploration in clinical research studies, where it benefitted from the ingenuity and research efforts of perhaps hundreds of clinicians and researchers to investigate and develop it as a diagnostic agent. Many liposomal NPs have begun to similarly exploit diagonal translation by seeking approval as simple drug-delivery vehicles, claiming efficacy equivalent to the existing unencapsulated drug and leaving investigation into the unique clinical properties conferred by the nanoformulation to future researchers. This avoids hinging the whole-cloth success or failure of the translation effort on the more uncertain aspects of the nanoscale functionality in humans. Dendrimers might take a similar translational pathway by seeking regulatory approval for a straightforward clinical indication, such as for drug delivery, and leaving clinical validation of its nanoscale functionality for post-market studies. NP researchers may choose to exploit the phenomenon of diagonal translation to facilitate the transition from the laboratory to the clinic; however, to do so requires a thorough

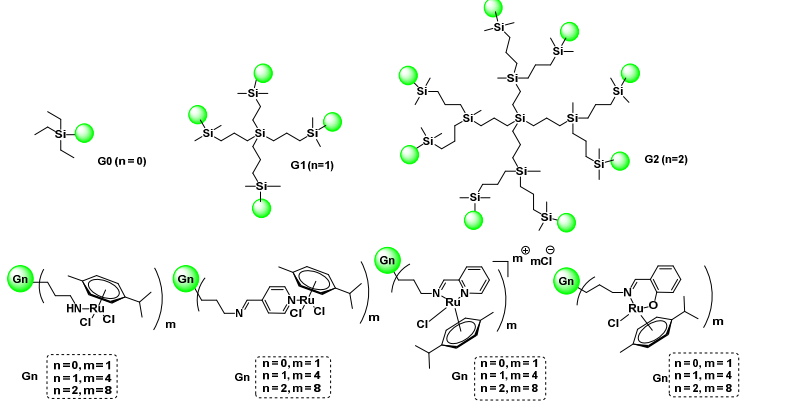
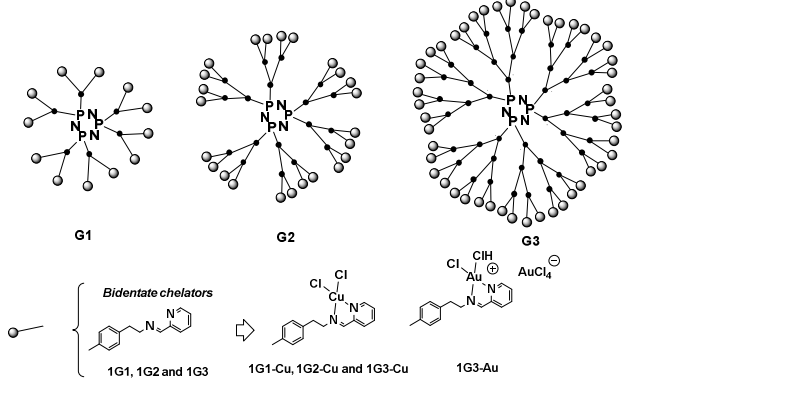
understanding of the phenomenon itself, and of the possible applications of the NP in question.

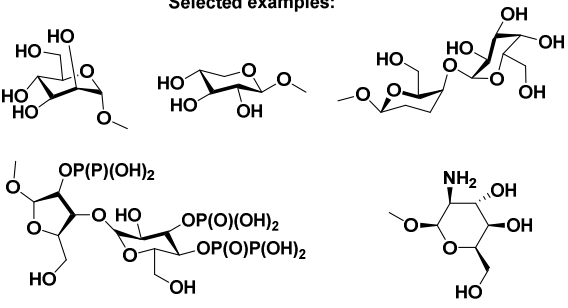
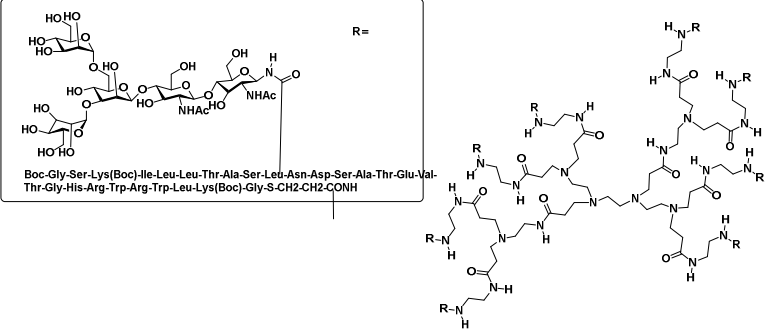
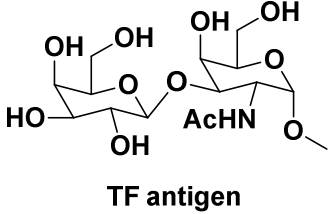
Table 2. Selected first-in-class dendrimers related to their generation, number and nature of active chemical groups on the surface, therapeutic applications, and development status.

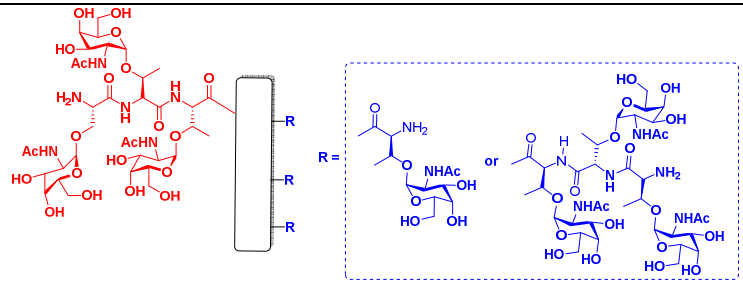
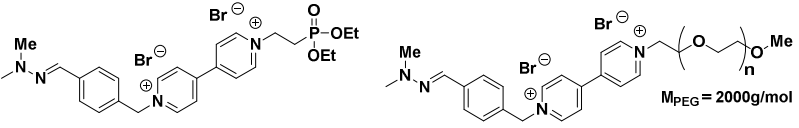
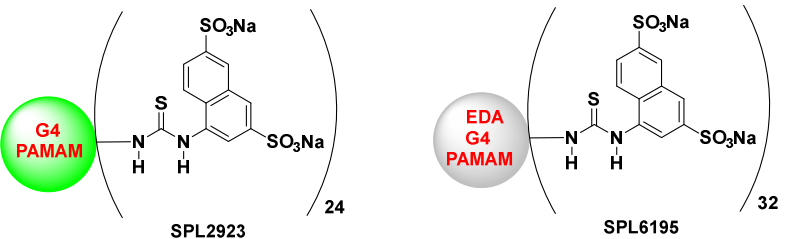
Dendrimer types	Surface moiety types	Number of active chemical groups on the surface	Therapeutic applications	Development status: Approved by regulatory agencies, preclinical stage	Reference
PAMAM	-NH ₂	G2-G5 PAMAM dendrimers G2 : 16, G3 : 32, G4 : 64 and G5 : 128	Antimicrobial Gram-positive and Gram-negative skin pathogens G5 > G4 > G3 > G2	Preclinical	43
PAMAM	-OH and -COOH	G4-PAMAM-OH : 64 and G3.5-PAMAM-COOH : 64	Antibacterial	Preclinical	93
PAMAM	 X = Pt(II), Cu(II)	G0-PAMAM : 4	Anticancer	Preclinical	94

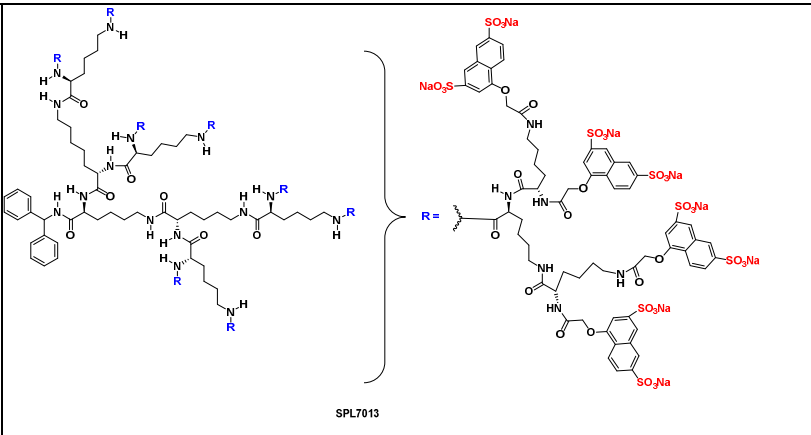
<p>Poly(propyleneimine) dendrimers (DAB)</p> 		<p>G2-DAB dendrimers : 8</p>	<p>Anticancer</p>	<p>Preclinical</p>	<p>95, 96</p>
		<p>4 and 8</p>	<p>Anticancer</p>	<p>Preclinical</p>	<p>97</p>
		<p>4, 8, 16 and 32</p>	<p>Anticancer</p>	<p>Preclinical</p>	<p>98</p>
<p>PAMAM metallodendrimers</p>		<p>2 (Zn(II)) + 4 (1,8-naphthalimide)</p>	<p>Anti-bacterial</p>	<p>Preclinical</p>	<p>99</p>

<p>Polyamide metallodendrime rs</p>	 <p>Generation 1</p> <p>Generation 2</p> <p>G1 and G2</p> <p>Me = Pt(II) and Pd(II)</p>	<p>G1 : 6 G2 : 6</p>	<p>Antibacterial and anticancer</p>	<p>Preclinical</p>	<p>100</p>
<p>Ferrocenyl metallodendrime rs</p>	 <p>n = 1 and 3</p> <p>= Fe(II)</p>	<p>4</p>	<p>Anticancer</p>	<p>Preclinical</p>	<p>101</p>
<p>Ruthenium (II) carbosilane metallodendrime rs</p>	 <p>I</p> <p>II</p>	<p>3 Ru(II) and 1 (spin-label unit), and 7 (Ru(II) and 1 (spin-label unit)</p>	<p>Spin-label probe technique in oncology</p>	<p>Preclinical</p>	<p>102</p>

<p>Carbosilane metallodendrimers</p>	 <p> $G_0 (n=0)$ $G_1 (n=1)$ $G_2 (n=2)$ </p> <p> G_n $\begin{cases} n=0, m=1 \\ n=1, m=4 \\ n=2, m=8 \end{cases}$ G_n $\begin{cases} n=0, m=1 \\ n=1, m=4 \\ n=2, m=8 \end{cases}$ G_n $\begin{cases} n=0, m=1 \\ n=1, m=4 \\ n=2, m=8 \end{cases}$ G_n $\begin{cases} n=0, m=1 \\ n=1, m=4 \\ n=2, m=8 \end{cases}$ </p>	<p> $G_0 : 1$ $G_1 : 4$ $G_2 : 8$ </p>	<p>Anticancer</p>	<p>Preclinical</p>	<p>103</p>
<p>Multivalent copper (II) and gold conjugated phosphorus- dendrimers</p>	 <p> G_1 G_2 G_3 </p> <p> <i>Bidentate chelators</i> $1G_1, 1G_2$ and $1G_3$ $1G_1\text{-Cu}, 1G_2\text{-Cu}$ and $1G_3\text{-Cu}$ $1G_3\text{-Au}$ </p>	<p> $G_1 : 12$ $G_2 : 24$ $G_3 : 48$ </p>	<p>Anticancer</p>	<p>Preclinical</p>	<p>104, 105</p>

<p>Glycoclusters and glycodendrimers</p> <p>(selected examples)</p>	<p>Selected examples:</p> 	<p>6 - >100 epitopes</p>	<p>Anti-inflammatory, antibacterial</p>	<p>Preclinical</p>	<p>106</p>
<p>PAMAM-glycopeptide dendrimers</p> <p>Selected example :</p> <p>For reviews see : 107 108 109</p>		<p>8</p>	<p>Extracellular matrix metalloproteinase inducer</p>	<p>Preclinical</p>	<p>110</p>
<p>PAMAM-glycodendrimers</p>	 <p>TF antigen</p>	<p>4-32</p>	<p>Antigenicity of the glycodendrimers to first prepare a vaccine conjugate</p>	<p>Preclinical</p>	<p>111</p>

Tetravalent glycodendrons		4	Immune responses with memory effects using carbohydrate cancer antigens	Preclinical	112
Phosphorus dendrimers	$-N(CH_2-PO_3HNa)_2$	$2 \times 6 = 12$	Anti-inflammatory	Preclinical	48
	$-NHR_2^{(+)}$	G0 : 6 G1 : 12	Anti-tuberculosis	Preclinical	113
	$-(NH-CH_2-CH_2-NEt_2)^+$	G3 : 96 G4 : 162 G5 : 324	Antiprion	Preclinical	45
Viologen phosphorus dendrimers		4-6	Alzheimer's disease and anti-bacterial activities (Gram ⁺ and Gram ⁻)	Preclinical	41, 114
G4 PAMAM and EDA G4 PAMAM dendrimers		G4 PAMAM: 24 (SPL2923) EDA G4 PAMAM : 32 (SPL6195)	Antiviral	Preclinical	115, 116

<p>Polylysine based-dendrimers</p>	 <p>SPL7013</p>	<p>64 sulfonate groups, SPL7013 (Vivagel®)</p>	<p>Micobicide, against bacterial vaginosis Antiviral agent</p>	<p>Developped and marketed by Starpharma (Australia)</p>	<p>39, 77</p>
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Conclusion and perspectives

Despite the global disruptions wrought by the COVID-19 pandemic the pharmaceutical industry managed to secure regulatory approval for 53 new therapeutics in 2020, with applications in oncology, neurology, and infectious diseases.¹¹⁷ A simple measure to evaluate the R&D productivity of the pharmaceutical industry is the number of new drugs (NDEs) introduced to the market. All studies agree that R&D productivity has decreased considerably over the past few decades commensurate with a decline in return on investment.¹¹⁸ These new approaches involving new technologies in general and nanotechnologies in particular has sparked a rapidly growing interest in solving issues linked to traditional treatments. Importantly, for instance, is the development of nanomedicine and consequently nanomaterials in immunoncology.¹¹⁹ In this challenging therapeutic realm, several types of NPs for clinical use were developed including liposomes, albumin-bound nanoparticles, PEGylated proteins, polymeric micellar nanoparticles, metal nanoparticles, C-dots, and dendrimers. Carrier-linked prodrugs were also developed as anticancer chemotherapeutics.¹²⁰ These nanoparticle-based therapies were used as nanocarriers in cancer therapy to improve the PK/PD of drugs-loaded nanoparticles^{121,122,123} from large pharmaceutical and small biotech companies. An interesting example is the huge variety in the nanoformulation of paclitaxel.¹²⁴ While dendrimers have been making steady progress as biocompatible nanoscale delivery platforms, they remain in their infancy as drugs in and of themselves.¹²⁵ To the best of our knowledge, two biologically active dendrimers were described for clinical uses despite a very large number of publications. A very small number of nanoparticles in general and dendrimers in particular have crossed the ‘valley of death’ between the early-stage research and clinical adoption.

Dendrimers face many barriers to clinical translation, as has been analyzed in several recent studies.^{28,30} These challenges can be understood in light of the concepts of nanoscale versus clinical multifunctionality and diagonal translation as illustrated by Guidolin and Zheng²⁶ and in combination with the first-in-class versus best-in-class nanoparticle development strategies.

We propose that the development of first-in-class dendrimers as drugs themselves with the potential to confer clinical multifunctionality may represent the next generation of precision (personalized) medicine, and will pave the way for the introduction of nanomedicines into more regular clinical

use.²³ Importantly, the development of dendrimers as active drugs *per se* represents a new strategy for determining the molecular mechanism of action of these dendrimers. In this direction, Figure 6 shows the overlapping of specific drug chemical spaces (small molecules, macrocycles, antibodies, and dendrimers active *per se* etc.) *versus* target types, ligandability, and the nature of ligands target types as firstly highlighted by the company Arvinas¹²⁶ and by Ottl et al.¹²⁷

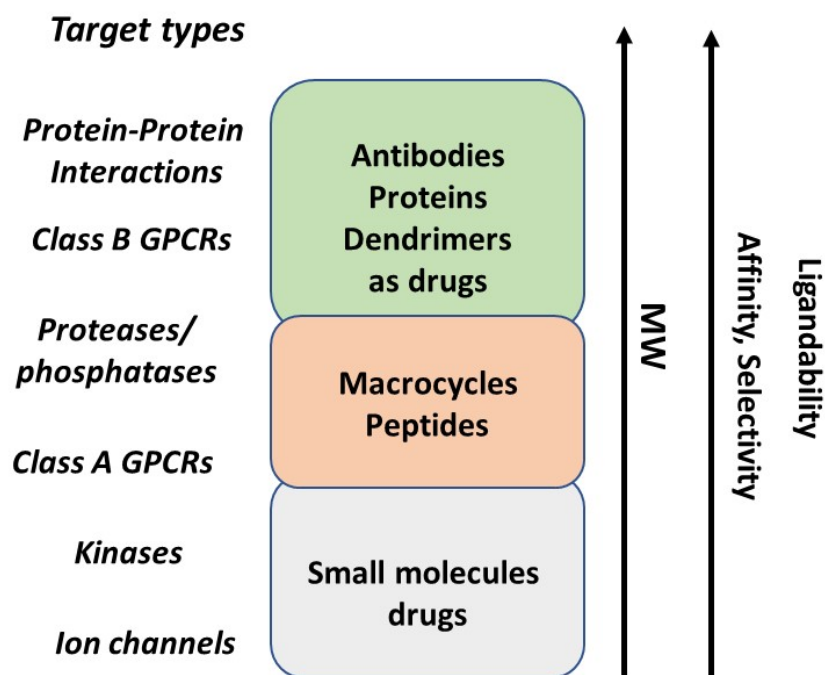


Figure 6. Representation of drug chemical space (small molecules, macrocycles, antibodies, and dendrimers active *per se*) versus target types and ligandability.

A recent example of mechanism of action discovery in the dendrimer space is seen in the work done by Mignani, Majoral, Shi et al., who developed FIC phosphorus dendrimers and dendrons bearing copper(II) and gold(III) (Table 2) as novel and potent *in vitro* and *in vivo* anticancer agents.¹²⁸ In addition, the development by Shi et al.,¹²⁹ of a non-invasive UTMD (ultrasound-targeted microbubble destruction) technique promoting the magnetic resonance (MR) imaging and chemotherapy of the pancreatic tumor using phosphorus dendrimer-copper(II) complexes as a drug is an example of the potential clinical multifunctionality possessed by dendrimers.

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Conflicts of interest

The authors declare no competing financial interest.

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