Nanomedicines in paediatric therapy: tribulations and the road ahead

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Abstract

Nanotechnology has emerged as a critical technique for overcoming medicines' primary (bio)pharmaceutical disadvantages and enabling active or passive targeting of certain cells and organs. Most paediatric treatments are based on adult clinical experience. However, there is a solid concept that medication pharmacokinetics and therapeutic outcomes differ in children and adults. The interaction of certain medicines with their target receptors varies with the maturity of various organs and systems. Usual observations are seen for adverse and toxic side effects, and so the implementation of innovative technologies (e.g. nanotechnology) in the paediatric population is very difficult in this environment. This article aims to deliver an overview of numerous initiatives to utilise nanotechnology to cure illnesses in children. We first discuss basic in vitro research through preclinical and clinical trials aimed at treating paediatric infectious illnesses and solid tumours using nanotechnology, despite little existing literature on this subject. Finally, future perspectives of nanomedicine for the paediatric population are elaborated.

Key words: nanotechnology, nanomedicine, paediatric diseases, paediatric cancer, cancer.

Introduction

Nanotechnology has emerged as a critical technique for overcoming fundamental (bio)pharmaceutical issues like decreased physicochemical stability, low aqueous solubility, and inadequate bioavailability [1, 2]. Nano-drug delivery systems can specifically target the cells and tissues, thereby augmenting the total drug payload at the intended location of the body and limiting the adverse effect by reducing the direct systemic exposure [3, 4]. Moreover, nano-formulations have been demonstrated to enhance localized medication delivery in areas protected by physiological or anatomical barriers, using alternate administration methods (e.g. inhalation). The ability of nanomedicine to enhance illness detection and therapy has been well proven, regardless of its level of complexity. Consequently, despite regulatory requirements, many nanomedicines have already reached the market [5, 6]. All of them, however, are intended for

adult usage. Still, there is no nanomedicine-based therapy approved for the paediatric population.

There are currently no authorized paediatric nanomedicines because the development of paediatric therapies has typically relied on prior experience in adults, which is still limited to the majority of the nanotechnology approaches. The use of recently developed regulatory initiatives, for example the paediatric investigation plan, which promotes particular studies in paediatrics in order to obtain the required data to gain clearance for a new medicinal product, will make it easier to get medicines approved for children. Because of the progressive growth and maturation of many organs, children have differences from adults [7, 8]. In the event of illnesses that affect children and adults, nanomedicines must first be modified for paediatric usage, which may need the development of a new pharmacological formulation, before being clinically tested in children. Furthermore, nanomedicines must be created specifically for illnesses unique to children or that have significantly higher morbidity in children [9]. Despite the rapid success of nanomedicine for adults, these realities, unfortunately, clash with the complexity of the segmented paediatric market and the difficult clinical studies that deter academic and industrial researchers from investigating nanomedicine for paediatric population.

Cancer is the second most common cause of mortality among children under 14 years old [10]. Paediatric cancer has been a prominent study area since the mid-1970s, and new research on the issue often emerges. In children under the age of 19 years, the death rates for a variety of malignancies have decreased significantly during the past 3 decades [11]. Nevertheless, despite current advancements, the 5-year mortality rate for youngsters with tumour remains as high as 26%, and several lives endure long-term unfavourable consequences that diminish their standard of living [12]. Presently, chemo is frequently used to treat juvenile cancer, despite its potential for adverse effects and damage to normal tissues. Due to their varying metabolic rates and undeveloped organs, children and adults have different tolerable doses, making it more difficult to determine the ideal dosage. The combination of 2 or more chemotherapeutic medicines has remained mostly unchanged over the past 2 decades, to prevent the drug resistance frequently induced by monotherapy. However, because organs and tissues develop fast in children, they may respond differently to the medicine at various stages of development. Consequently, the childhood cancer survival rate remains poor.

This article aims to outline the many initiatives to utilise nanotechnology to cure illnesses in children. We first discuss basic *in vitro* research and preliminary and clinical studies of the treatment of juvenile infective illnesses and solid tumours using nanotechnology, despite the scant accessible literature on the subject. The future of paediatric nanomedicine is then explored.

Nanomedicine for infectious diseases in the paediatric population

Even though a wide range of anti-bacterial agents are available, the management of infections has become a growing problem for contemporary medicine as resistant bacteria arise. Because of the reasons stated above, the condition is considerably more severe in the event of poverty-related illnesses and much more so in the case of the paediatric patients. The early advances made at the intersection of nanomedicine and paediatric HIV, tuberculosis, and malaria treatment, the 3 diseases that take the most lives each year, will be reviewed in advance.

HIV/AIDS

With about 2.5 million fatalities each year, HIV/AIDS is the most devastating illness of current times [13]. In 2020, around 150,000 children (0–9) were newly infected with HIV, with a total of 1.03 million children who have HIV [14]. Due to the difficulty of clinical studies, the number of antiretroviral drugs (ARVs) approved for use in children is lower than that of adults, although the pharmacokinetic information is relatively inadequate [15]. The absence of approved liquid, chewable [16], dispersible [17], and orodispersible formulations [18, 19], as well as the creation of paediatric fixed dose combinations (FDCs) [20], are further disadvantages. Regardless of the approach chosen, the manufacturing procedure must be counterbalanced to keep medicine prices within reasonable bounds for patients [21]. Because the disease affects both adults and children, the progression of nanomedicines for HIV prevention might be useful to all patient subpopulations. Despite this, there are surprisingly few research projects aimed at developing nanotechnology-based anti-HIV medications overall, and specifically for kids.

Nanosuspensions are pure drug nanomaterials dispersions in a liquid pharmaceutical carrier maintained by emulsifiers [22, 23]. They are the simplest basic nano-formulation, and because of the continuous increase in the surface area due to the smallest particle diameter, they may achieve a significant increase in dissolution rate and oral bioavailability. Despite the promise of this technology to generate liquid solutions that would allow for simpler dosage adjustment and ingestion, in HIV, only a small number of ARV nano-dispersions

have been examined, none of which have been tested in children [24]. Polymeric micelles (PMs), a form of self-assembly nanomaterials created by complexing polymeric amphiphiles [25], have been evaluated with various routes of administration, e.g. parenteral [26], oral [27], intranasal [28, 29], and ocular [30], to augment the aqueous solubility of lipophilic drugs. A variety of PM-based medicines for treating various malignancies are now undergoing clinical trials [31]. To develop a sustainable and cost-effective water-based paediatric formulation, our group assessed the entrapment of the very first ARV efavirenz (EFV) included in PMs comprised of pristine and chemically changed poly (ethylene oxide)-b-poly(propylene oxide) block copolymers (PEO-PPOs) [32–34]. In mixed micelles, the drug's solubility was improved from 4 g/ml to 34 mg/ml, reflecting an 8430-fold increase [34–36]. The physical stability of EFV-loaded PMs was shown under a variety of storage settings, including severe dilution in gastrointestinal-like medium [34–36]. The pharmacokinetics of oral EFV were first evaluated in rats and matched to those of a typical extemporaneous simple syrup suspension and an oily solution that replicated the sole commercialized paediatric dosage of EFV in a medium-chain triglyceride (MCT), Miglyol [33, 34].

Regardless of nanotechnology's potential to develop paediatric HIV therapy, other issues appear to be more pressing. For example, EFV causes a condition known as burning mouth syndrome (BMS), which can be alleviated by using a mix of tastes, sweeteners, and essences [35]. As a result, nanotechnologies must address other problems just as important in ensuring patient compliance and treatment regimen compliance.

Three factors that may influence the clinical translation of novel medications should be discussed at this time. The continual training of individuals assigned to assess clinical procedures is required for therapeutic innovation. Otherwise, the evaluation would be insufficiently rigorous, putting the participants' safety at risk. In contrast, patients may be denied access to potentially beneficial and safe products if the "precautionary principle" occurs due to the regulatory agency's lack of competence.

Tuberculosis

Tuberculosis (TB) is the second most lethal illness after HIV, with 1.5–1.7 million people dying each year [37, 38]. Although TB generally affects the airways, untreated or resistant strains have been seen to spread the illness to other organs [39]. Isoniazid, pyrazinamide, rifampicin, and ethambutol are used in the first 60 days of conventional TB treatment, while RIF and INH are used in the last 4 months [40]. The effectiveness of TB treatment is closely linked to strict adherence to treatment approaches.

Even though ordinary tuberculosis infection can be treated, it nevertheless accounts for more than 25% of avoidable deaths and 2.4% of all fatalities worldwide [41]. Paediatric tuberculosis accounts for just 5% of all infections in industrialized nations, but it causes 20–40% morbidity in underdeveloped countries, with 130,000 children dying each year [42]. Because of the difficulty of diagnosis and the absence of commercially accessible preparations with enhanced (bio) pharmaceutical efficacy [43], containing RIF/INH FDCs, children constitute a high-risk subpopulation, similar to HIV. Indian firms have established a variety of double and triple FDCs, but none have completed clinical studies [44]. Furthermore, some of these advancements ignore the fact that the gastrointestinal 284 tract's circumstances may accelerate the breakdown of several first-line medicines when they are taken orally. For example, in gastric acid fluids, rapid hydrolysis of RIF results in 3-formyl RIF SV, a compound with little anti-TB action *in vivo* because of the low oral bioavailability [45]. INH catalyses this route, resulting in a 30–50% increase in the degradation rate [46, 47]. As a result, INH-mediated decrease of oral bioavailability of RIF is a major worldwide issue [48], and novel nanomedicines may be able to help.

Only a limited research organizations worldwide, mostly in poor countries, have focused on the progression of nanotechnology-based paediatric anti-TB medications [43]. Khuller and Swai's groups explored the entrapment of anti-TB medicines into nanomaterials and evaluated their efficacy in murine TB models via oral administration [49, 50]. Due to the preclinical testing done on infected TB animals, these findings were extremely reliable. These nanomedicines show great promise in replacing the present daily delivery routine with a single 7–10-day administration. Even though these advancements were not designed specifically for children, any effective bench-to-bedside therapy could benefit the paediatric population. To adhere to PIP regulatory regulations, further clinical trials in children are required. Our group has spent the previous 5 years looking on the RIF encasement inside various forms of PMs [51]. The drug's aqueous solubility was enhanced by up to 5.4 times after encapsulation; however, RIF-loaded PMs suffered progressive subordinate grouping, as a result of which physical stability deteriorated with time. As a result, a cryo-protected lyophilization method [52] was devised. *In vitro*, PMs not only chemically stabilised RIF in the presence and absence of soluble INH, but they

also lead to considerably higher RIF bioavailability when taken orally (by up to 3.3 times) than a drug solution mixed with INH in a 3/2 weight ratio [52]. This type of nanotechnology approach might be used to create the first RIF/INH liquid paediatric FDC.

Malaria

Malaria is the parasite illness that causes the most morbidity and mortality worldwide [53]. In 2011, nearly 3.3 billion people contracted malaria, with 80% of cases and 90% of fatalities occurring in Sub-Saharan Africa [54]. The most severely affected subpopulations are children under the age of 5 years, as well as pregnant mothers. Malaria can be prevented and cured, but it resulted in the death of more than 6 million children in 2010 [54], which comprised 20% of the paediatric deaths in Africa [55]. Artemisinin-based combination treatments (ACTs) are the first-line therapy for simple falciparum malaria in children, which come in difficult-to-swallow tablets [56]. The WHO has recommended novel formulations of oral ACT paediatrics products in this context. The creation of suspensions, rapidly dissolving tablets, and granules comprising lumefantrine/artemether [57, 58], pyronaridine/artesunate [59], and mefloquine/artesunate is among the most significant advances. Various nano-formulations have been researched for the development of novel antimalarial agents, but only a few of these were focused on the paediatric population [60]. CDs most likely focus on the vast use of the nanotechnological approach, specifically the masking of the bitter taste of antimalarial agents. Shah *et al*., for instance, enhanced the taste of an artemetherin liquid formulation [61]. Complexes of primaquine phosphate were used in a similar manner to create powders for resuspension [62]. As a result, reduction in RIF oral bioavailability caused by INH is a huge global concern [63], and novel nanomedicines may be able to help.

Recent developments in nanomedicine for paediatric cancer

Nanomedicine plays a critical role in the antitumour activity of Paediatric Cancer. Figure 1 highlights the various therapeutic strategies of nanomedicine in cancer, and below we explain them in detail.

Blood cancers

Leukaemia

Leukaemia is the most prevalent cancer in children, accounting for roughly 28% of all paediatric malignancies. White blood cells that are abnormal, which come from organs that generate blood cells, are the hallmark of the illness.

Leukaemia has been treated with nanomaterials made of lipids. To combat multidrug resistance, in one study, solid nanoparticles based on lipids were employed to transfer mitoxantrone and a P-glycoprotein (P-gp) suppresser element [64]. Overexpression of P-gp is thought to disrupt the multidrug resistance mechanism. As a result, combining the P-gp and mitoxantrone inhibitors can have a synergistic impact on inhibition and therapeutic effects. This nanocarrier, which has a negative surface charge and a size of 120 nm, was successfully loaded with the medication mixture and remained colloid stable after delivery.

Immunotherapy is another cancer treatment method that involves activating or improving im-

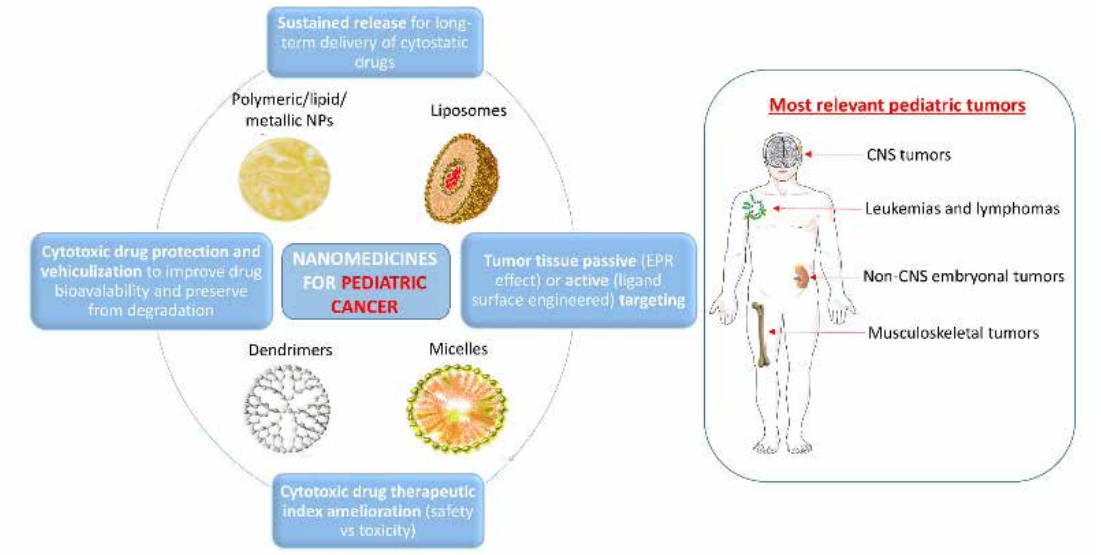

Figure 1. Nanomedicines as treatment options for paediatric malignancies

mune cells' capacity to recognize and destroy tumour cells. One research group investigated the utilisation of ionizable nanomaterials for mRNA transport in CAR T cell therapy [65]. T cells are extracted from the individual and modified by inserting DNA or RNA into them to create CARs on their surfaces. It is an FDA-approved treatment for acute lymphoblastic leukaemia (ALL).

Lymphoma

Lymphoma is a lymphatic system cancer of the lymph glands and spreads to certain other tissues through lymph fluid. Lymphoma is the third most recurrent kind of tumour in youngsters, after brain cancers and leukaemia. Every year, 2200 individuals under the age of 20 years in the United States are diagnosed with lymphoma. Lymphoma and non-Hodgkin lymphoma account for around a quarter of all paediatric cancers [66]. Adults with lymphoma are frequently treated with the anti-CD30 antibody-drug combination brentuximab and the anti-CD20 antibody rituximab. However, no targeted therapies are authorized for use in lymphoma patients under the age of 18 years [66].

ALCL, the most frequent form of T-cell lymphoma in children, comprises an activated hazardous ALK oncogene and elevated amounts of CD30 cell surface expression. Nanoparticles treated with doxorubicin and ALK oncogene-specific siRNA and generated using RNA-based CD30-specific aptamers were used to treat ALCL with precision. Thanks to the aptamers that are conjugated, the nanomaterial accurately targets ALCL cells, and the loaded gene curing agent siRNA and chemotherapeutic drug doxorubicin enhance their tumour killing potential [67].

Bone cancers

Osteosarcoma

Bone tumours primarily affect older children and teenagers, accounting for around 3% of all paediatric malignancies. Osteosarcoma is the most prevalent kind of bone tumour, and it has a disproportionate impact on children. It affects young individuals (10–30 years old) and accounts for 2% of all paediatric malignancies [68]. In this group, most osteosarcomas are highly malignant tumours with a dismal diagnosis [68]. A distant tumour that has migrated beyond surrounding tissue has a 5-year rate of survival of 27% throughout all ages, according to American Cancer Society data [69].

As with previous cancer therapies, nanoparticle administration to osteosarcoma cancers is a developing area of study that aims to improve targeted medicine delivery while minimising cellular and dosage damage. This is accomplished either via passive transport, which depends on the EPR outcome, or through active distribution, which employs the acidic pH of the osteosarcoma cancer environment and nanoparticle surface modification.

Due to their biocompatibility and surface alteration capabilities, Liposomes seem to be the most thoroughly examined vehicle for osteosarcoma treatment [70]. Because doxorubicin was integrated into liposomes, it improved the permeability of cells and cancer death of associated cells when it was administered free [71]. Some investigations have demonstrated that liposome nanocarriers may be optimised to release drugs at an osteosarcoma tumour's particular temperature and pH [72]. Others have investigated liposome PEGylation, which decreases nanomaterial re-absorption by the reticuloendothelial system, resulting in a prolonged half-life and a less optimum dose [73]. In a recent *in vitro* investigation, the combination of gemcitabine and clofazimine in nanoparticles was discovered to have synergistic effects. This double loading was accomplished by inserting the gemcitabine hydrophobic into the liposome core and the clofazimine hydrophilic between the lipid bilayers [74].

Inhibiting the synthesis of proteins by osteosarcoma cells using RNAi treatments, for instance siRNAs and microRNAs, has exposed potential and may be useful when combined with chemotherapies [75]. In contrast, the bioavailability and cellular absorption of potential nucleic acid carriers are hampered by their poor physicochemical qualities. A study on prospective biocompatible carriers, including Amy-g- PLLD [76], has been reported. Both alone and in combination with doxorubicin, PEGylated liposomes have been evaluated for siRNA delivery [77, 78]. In 2017, a study demonstrated that using chitooligosaccharides to improve drug delivery enhanced tumour cell engulfment, anti-cancer implications, and the rate of continued existence in mice models [79]. Curcum induced apoptosis with a rise in the concentration of markers, for instance sliced caspase and poly(ADP-ribose) polymerase and autophagy *in vitro*. Outcomes in vivo tailed a like pattern (Figure 2) [80]. Dhule *et al.* created a human OS tumour and cured it with conventional, HPCD-curcumin liposomes and empty liposomes. They performed haematoxylin-eosin staining and the DeadEndTM Colorimetric TUNEL test (Terminal deoxynucleotidyl transferase dUTP nick end labelling). Figure 3 A illustrates nuclei stained in dark blue haematoxylin and cytoplasm in pink eosin, while nuclei are lost in dead cells in tumours treated with liposomal curcumin (Figures 3 C and E), as shown by the black arrow, indicating that curcumin liposomes and curcumin itself cause cell death. Compared to Figure 3 B, the arrows in Figure 3 D and F suggest a substantial increase in apoptosis (brown regions). The brown spots designate the DNA-fragmented apoptotic area [80].

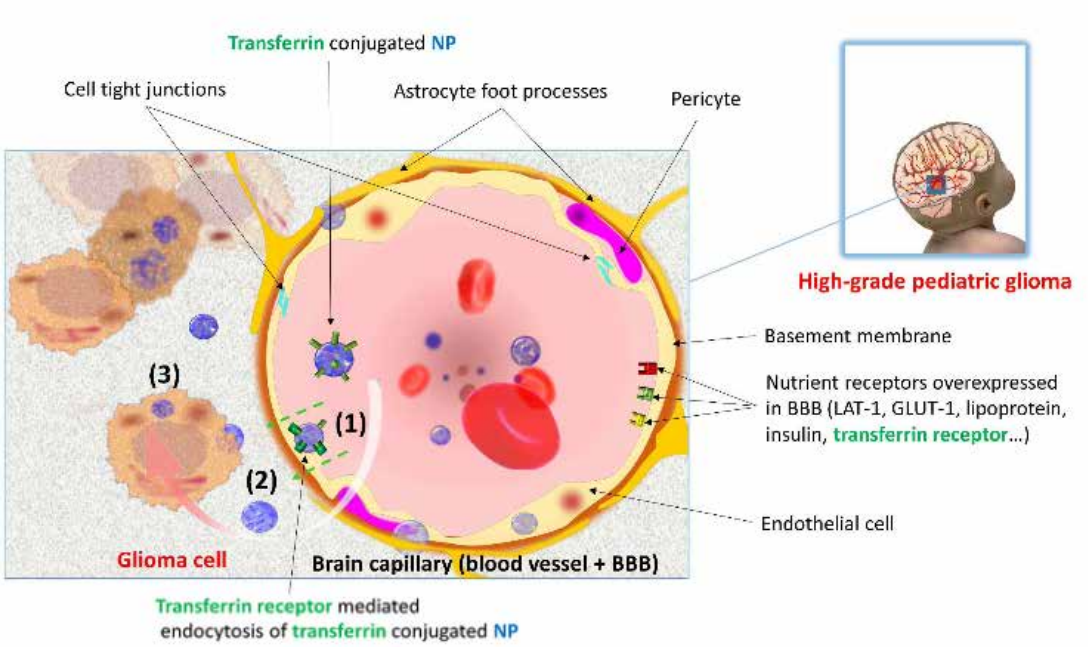

Figure 2. Nanomedicine crossing the BBB in paediatric cancer. (1) Nanomedicine ligands are recognized by receptors; (2) NPs extravasate into CNS; (3) Internalized NPs release their cytotoxic drug cargo, resulting in the demise of tumour cells. Reproduced with permission from [85]

Cancers of the central nervous system

Brain cancer

Brain malignancies are the second most prevalent malignancy in children, accounting for roughly 26% of all cancers in children. Brain malignancies are named after the cell type that gave rise to cancer and the location of the tumour in the brain. Surgery, radiation, and chemotherapy are used to treat them. However, brain tumours might make operation and the delivery of therapeutic medicines difficult, depending on their location.

The blood brain barrier

The blood brain barrier (BBB) is a compact barrier between the brain and the vascular system that protects the brain from potentially hazardous substances and infections while also regulating the flow of vital nutrients to keep a steady microclimate [81]. Endothelial cells with tight junctions, astrocytes, pericytes, and a persistent basement membrane make up the BBB. It is a semipermeable barrier with a strong expression level of many transporter protein sets that allow only essential small molecules such as oxygen to flow freely. Because the BBB is so effective, fewer medicines are effective, and the prognosis for paediatric patients with brain cancer is poorer [82]. Figure 4 illustrates the various approaches adapted by nanomedicine for crossing the BBB.

Molecular size appears to play a critical role in BBB penetration, according to the research. However, the size of molecules does not always affect BBB permeability [83]. The BBB prevents several tiny compounds with a molecular weight of approximately 100 Da from entering the brain, such as histamine [84]. Nevertheless, candidates may be able to pass if they interact with the BBB's primary transporters. It is believed that the activity of ATP-binding cassette (ABC) efflux carriers, for instance the (BCRP) breast cancer resistance protein, prevents many drugs from entering the brain [83].

The use of nanotechnology has aided in the delivery of medicinal drugs across the BBB. Gold, proteins, in the therapy and diagnostics of brain cancer, Lipids are being researched for use as cytostatic agents or medication transporters. The capacity to penetrate the BBB is influenced by 2 primary factors: nanoparticle size and surface. It tends to inhibit large particles, but a slightly positive surface charge might encourage particle–endothelial cell interaction [82]. Antibodies with a molecular weight of more than 500 kDa, such as intact IgG, commonly employed to cure malignancies, have poor BBB penetration [82]. Smaller antibody chains, for instance single-chain mutable segments or fragment antigen-binding (Fab), can reach the CNS more effectively.

In addition to diffusion, transcytosis mediated by ligands is being studied to transport drugs passing through the BBB. Despite the fact that the BBB is an extremely selective, Endothelial cell barrier that is semipermeable, the specific protein carriers produced on its membrane that permit

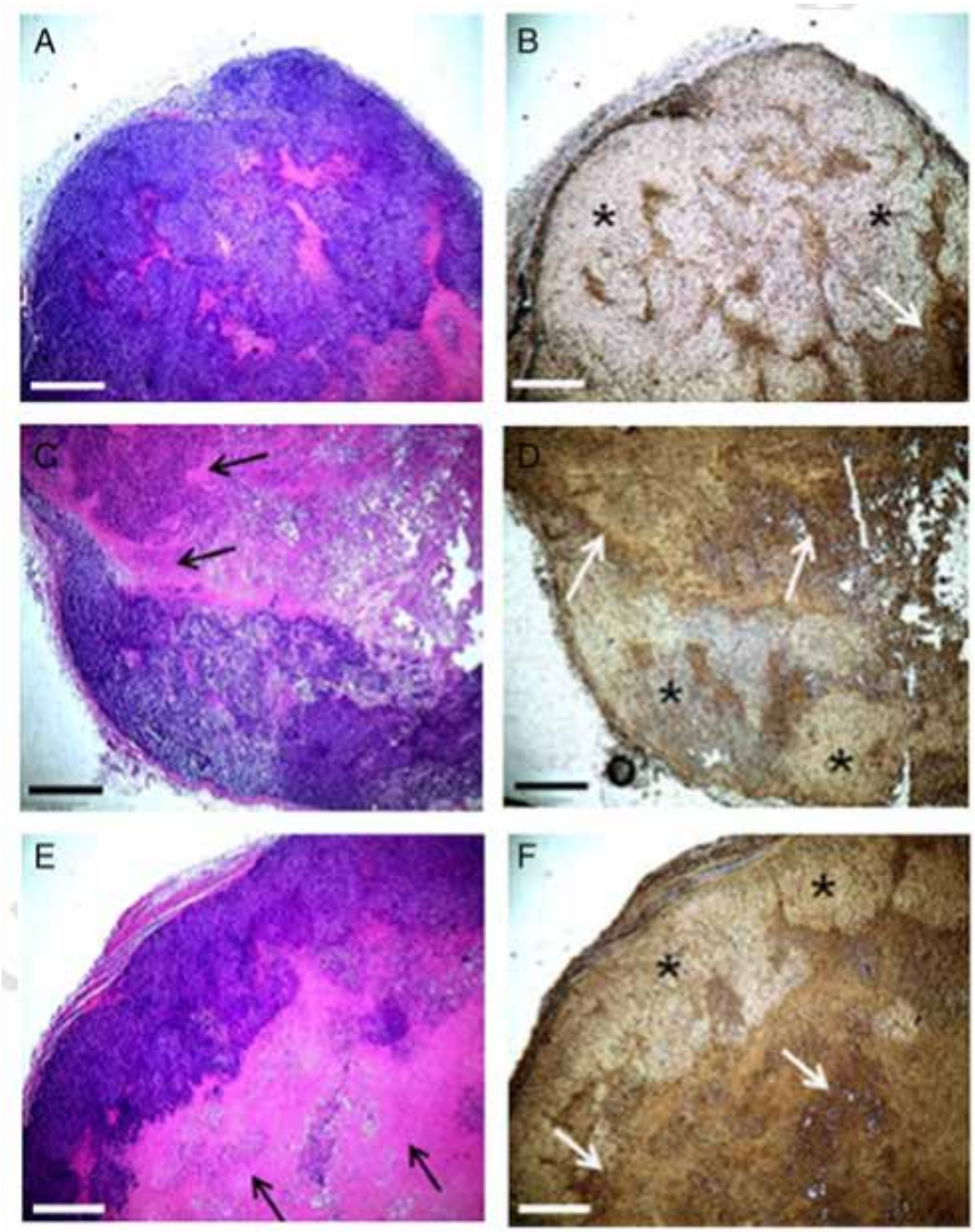

Figure 3. Liposomes containing curcumin cause cell death caused by apoptosis in a xenograft osteosarcoma model. Cancer cured with vacant liposomes (**A**, **B**), standard curcumin liposomes (**C**, **D**), and hydroxypropyl – CD-curcumin liposomes (**E**, **F**). Haematoxylin and eosin staining for tumour histology is shown in subfigures **A**, **C**, and **E**, while TUNEL staining for apoptosis detection is shown in subfigures **B**, **D**, and **F** – reproduced with permission from [80]

critical nutrients to be delivered to the brain are optimal objectives.

The transferrin receptor (TfR) controls iron delivery into the parenchyma of the brain, which is required for brain metabolism, neuronal conductance, as well as general brain tasks [85]. TfR is a remarkable and one-of-a-kind target because it is only produced on endothelial cells lining brain capillaries rather than on endothelial cells lining the arteries of other organs [86]. Transferrin receptor antibody is an appealing idea for medication delivery across the BBB because of its singular property. When combined with nanoparticles, for instance liposomes, penetration and BBB targeting would be greatly increased [87–89].

Similarly, to cross the BBB, cell-penetrating peptides (CPPs) have been used. CPPs enable the cellular absorption of materials ranging from

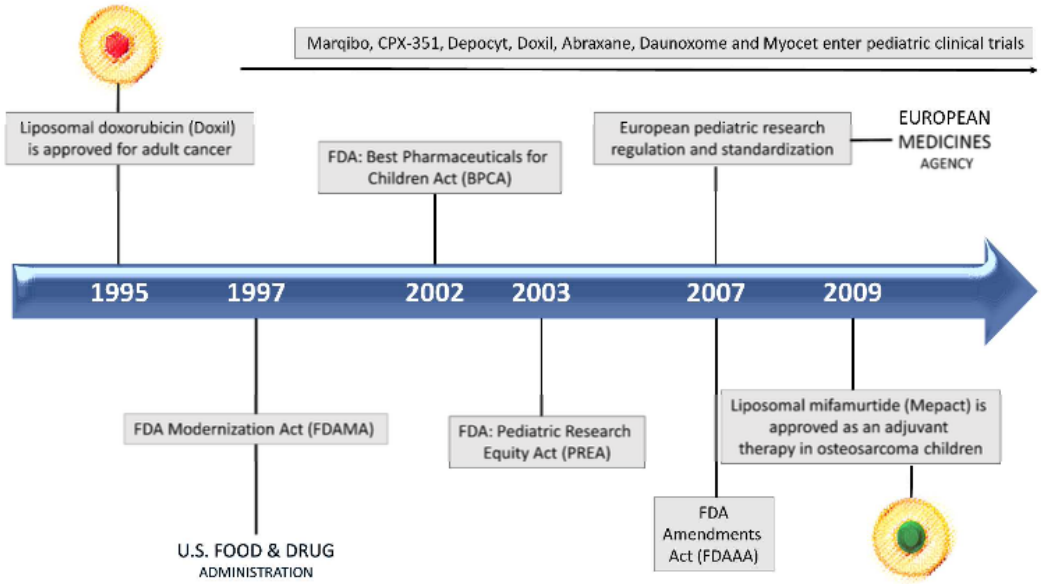

Figure 4. Timeline of nanomedicine development for paediatric cancers

nanoparticles, through tiny chemical compounds, to big pieces of DNA. Wang *et al.* investigated the effectiveness of Tf-LPs and CPPs loaded with doxorubicin in the treatment of glioblastoma. In 2 kinds of glioma cells, this 120 nm nanoparticle with a zeta potential of 6.81 mV demonstrated increased cellular absorption and decreased toxicity when compared to free doxorubicin [90].

Amplification of the EGFR expression, which occurs in roughly half of all malignant gliomas [91, 92], is another potential marker. Human epidermal growth factor receptors are all members of the ErbB family of receptor tyrosine kinases [93]. The use of EGF, EGFR's natural ligand, might be a way to target all types of tumour cells, including those that express wild-type and mutant EGFR. The coupling of EGF to the nanoparticle may allow for targeted glioma therapy [94, 95].

Due to the brain's distinctive environment, which may be considered an immune-privileged zone, distinct in comparison to the rest of the body, immune cells are prevented from accessing the brain [96, 97], and so immunotherapy is increasingly being utilised for brain tumours more than for other tumour forms. As a result, microglia occupy a prominent position inside the brain. They are pro-tumourigenic under certain conditions, such as excessive synthesis of growth factors and lack of T-cell regulation. In addition, most brain tumours contain an extracellular structure that inhibits the migration and activation of T cells, hence preventing their movement and proliferation [98].

Glioma

Glioma is a kind of childhood brain cancer formed by glial cells, which maintain and feed the neurons in the brain [99]. To treat glioblastoma, a micelle of folacin-modified poly(e-caprolactone) was created to transport luteolin, a vegetable-derived xanthone with broad-spectrum anticancer effects [100]. Folate acids have been conjugated to the nanoparticle's surface so that it could bind to the folate receptor, a glycoprotein that is overexpressed in numerous tumour tissues. In glioma tissues, luteolin-enriched folate acid-refined micelles induce much more cell inhibition and death than free luteolin and micelles devoid of folacin alteration [100].

Endothelial cells have an increased expression of TfRs of the BBB and gliomas. Fan *et al.* proposed a trans-BBB supply approach using protein-coated iron oxide with human H-Ferritin and L-Ferritin nanomaterials (HFns) to target BBB endothelial cell TfRs and cause transcytosis [101]. The nanomaterial exhibited sufficient drug-loading capacity and double cancer-targeting capability. TfR-mediated transcytosis carried them beyond the BBB in the endosome, where they were identified and entered glia cells through human H-ferritin receptor-mediated tumour targeting.

Radiotherapy is an essential element of tumour treatment. However, radiation-induced side effects and confrontation pose clinical constraints. Combining irradiation with various therapeutic drugs that obstruct certain DNA reparation pathways might provide greater therapeutic success than monotherapy with a lesser radiation dose that minimises possible side effects. By employing nanomaterial-based transfer of siRNA to inhibit the appearance of Ape1, an enzyme that participates in the excision of the base restoration pathway, Kievit *et al.* discovered a method of sensitising paediatric cancer cells, such as ependymoma

and medulloblastoma cells, to radiation [102]. This chitosan, PEG, and polyethyleneimine-coated superparamagnetic iron oxide nanomaterial may bind to siRNA to prevent its deprivation. The medulloblastoma and ependymoma cells treated with siApe1 showed a 75% decrease in Ape1 expression and an 80% suppression of Ape1 activity, indicating that siApe1 may be an efficient delivery strategy. Figure 4 summarizes the various breakthroughs in nanomedicine for paediatric cancer treatment.

Challenges of designing nanomedicine for the paediatric population

Children are not merely little adults, according to doctors throughout the world [103]. This is not a cliche of demagogy; it is founded on scientific research that shows that children and adults have different medication absorption, biodistribution, metabolism, and excretion patterns [104]. Children also have varied pharmacodynamics as a result of the various interactions of medicines with their biological targets [105]. In this perspective, it is obvious that treating illness in children cannot be reduced to a simple dosage modification based on body weight/surface area [106]. The paediatric subpopulation is also divided into subgroups based on biological and metabolic differences, including premature baby newborns, term newborn babies (0–27 days), preschool children (2–5 years), toddlers and infants (28 days–23 months), school-aged children (6–11 years), and teenagers (12–16/18 years) [107]. Various gastric pH and passages, motility of intestine, and bile salt conjugations and transports are shown in each sub-category [107]. In addition, cognitive development may influence the formulation suitability (for instance, in the case of inhalers) [108] and clinical trial possibility [109]. Paediatric clinical studies, for example, are more difficult because of clinical, scientific, ethical, technological, and logistical issues that have consistently hampered progression [110, 111]. Furthermore, the toxicological implications of nanoparticle exposure, particularly by inhalation, should be extensively studied, because children have higher particle accumulation in the lungs than adults [112]. For instance, various liposome compositions have proven biocompatibility, and some nano-DDSs have been evaluated in adults [113]. However, there is comparatively little information on the safety in youngsters. Other methods, for example carbon nanotubes, are more contentious, and their therapeutic use appears implausible [114]. All of these issues diminish the fragmented paediatric market's flexibility and proximity, placing children at the top of the vulnerability scale [115].

Future perspective

The global nanomedicine sector was valued at $72.8 billion in 2011, as per a BCC investigation, with anti-tumour medications leading the way. The market is projected to grow at an annual pace of 12.5% until 2016, when it will be valued $130.9 billion. In this globalized world, nanomedicine looks to be an auspicious tool for enhancing the treatment of paediatric disease [116]. In 2008, the Mattel Children's Hospital of the University of California, Los Angeles established the ground-breaking NanoPediatrics Programme, and in 2011, Children's Healthcare of Atlanta and Emory University School of Medicine established the Center for Pediatric Nanomaterials, which are examples of this potential and foresight. Other specialized institutes, such as the University of Novel South Wales' Australian Centre for Nanomedicine (Sydney, Australia), have dedicated one of their revolutionary initiatives to discovering new treatments for neuroblastoma, the most prevalent tumour in children under the age of 5 years. Everything designates the significance of this avenue of investigation. At the same time, we should be persuasive and underline that translation from the laboratory to the bedside is a long and complicated process. Associated with the amount of research funds assigned to this area, there are fewer nanopharmaceutical materials available on the market. The PIP is a government initiative in the United States that funds research on paediatric therapies [117, 118] and also in Europe [119], which may increase advances in paediatric nanomedicines. Formation of the Paediatric Committee-Formulation Working Group of the European Medicines Agency is an exciting way to stimulate the creation of novel paediatric formulations and, in this example, the use of nanotechnologies to enhance efficiency. In recent years, it has been gratifying to see the emergence and consolidation of programmes that address fundamental barriers to paediatric therapy, for instance the Pediatric Formulation Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development [120], and the European Paediatric Formulation Initiative (EuPFI). GRIP (Global Research in Paediatrics – Network of Excellence), as well as the Global Research in Paediatrics – Network of Excellence (GRIP) [121]. These organisations examine and improve the taste and palatability of medications, which is a key problem in paediatric treatment [121]. Unrequited is if these creativities will be willing to support (or not) the development of multi-disciplinary groups to solve the myriad challenges associated with the use of nanomedicine to children. Due to commercial constraints, we believe that the future of paediatric nanomedicine is inexorably linked to advances in the use of these advanced medica-

tions in adults. This is reinforced by nanomedicine's lack of a reliable regulatory regime [122], which, from an ethical position, encourages the usage of the "Principle of precaution", limiting the use of nanotechnology on youngsters to the long term and only after lengthy and painstaking studies [123]. In contrast, many illnesses have a very high morbidity rate among youngsters, necessitating particular care and dedication that transcends commercial considerations to offer better treatment for everybody. The creation of research groups in academia and business that focus on the targeted and interdisciplinary treatment of each illness appears to be the most successful method for them. Instead, the present gap between adults and children would become much wider, placing paediatric patients even farther behind.

The role of nanomedicine in the neonatal period is of extreme interest, and various research groups are actively investigating the potential role of nanomedicine in the neonatal period. However, a previous study suggests that early exposure to the nanomedicine may induce inflammation and other pathological conditions [124]. Another study investigating the use of nanoparticles in the lungs of babies discovered that alveoli develop through secondary septation, alveolar flow becomes turbulent, and chaotic mixing sets in, considerably boosting particle deposition [125]. Despite the keen interest, there are no encouraging results. The researchers are actively investing the optimized kind of nanoparticle and understanding the interaction of nanomedicine with the different organs and physiological changes in the infant.

Concluding remarks

Nanotechnology has emerged as a critical technique for overcoming fundamental (bio)pharmaceutical issues like low aqueous solubility, reduced physicochemical stability, and limited bioavailability. Nanomedicine brings sustainable results for treating infant illness ranging from infection to various cancers and HIV. However, there are still many obstacles in translating those therapies and conducting clinical trials. Moreover, designing appropriate nanoparticles and minimizing their toxicity is still a challenge that needs to be solved. Although the success rate and growth of nanomedicine in the paediatric population is slower than in adults, it holds great potential and will revolutionize the field.

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Conflict of interest

The authors declare no conflict of interest.

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