Review Article

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Therapeutic nanomedicine surmounts the limitations of pharmacotherapy

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Abstract: Science always strives to find an improved way of doing things and nanoscience is one such approach. Nanomaterials are suitable for pharmaceutical applications mostly because of their size which facilitates absorption, distribution, metabolism and excretion of the nanoparticles. Whether labile or insoluble nanoparticles, their cytotoxic effect on malignant cells has moved the use of nanomedicine into focus. Since nanomedicine can be described as the science and technology of diagnosing, treating and preventing diseases towards ultimately improving human health, a lot of nanotechnology options have received approval by various regulatory agencies. Nanodrugs also have been discovered to be more precise in targeting the desired site, hence maximizing the therapeutic effects, while minimizing side-effects on the rest of the body. This unique property and more has made nanomedicine popular in therapeutic medicine employing nanotechnology in genetic therapy, drug encapsulation, enzyme manipulation and control, tissue engineering, target drug delivery, pharmacogenomics, stem cell and cloning, and even virus-based hybrids. This review highlights nanoproducts that are in development and have gained approval through one clinical trial stage or the other.

Keywords: Nanotechnology; Nanomedicine; Nanoparticle; Therapeutic; Medicine

1 Introduction

Nanotechnology has stayed with us for more than a decade now, and governments as well as independent funding organizations/agencies have pumped billions of US dollars into research that has produced tens of thousands of published papers. But what exactly are we talking about? This question is pertinent because the very next follow-up issues are considerations on how to carve-out "Nanoscience" and the associated fields into a different discipline rather than remaining an integrated concept in other disciplines. For instance, nanomedicine is already beginning to produce other sub-fields under our watch even though it is yet to be fully pronounced as an accredited discipline of its own. Go to the archives and you will see a whole lot of journal papers, books, news, editorials and the likes on nanomedicine addressing basic issues of clinical applications. Nonetheless, all that "Nanoscience" and the associated fields are trying to convey is that, in solving problems, "smaller" (specifics or details) is better than "bigger" (generalization or broad). In nanotechnology, the fact is that science has employed technology to get a job done. It has been observed however, that in the course of research that science and technology, in trying to find a solution to a particular problem or challenge, damage in another form is done [1-3]. This is obvious in the side-effects associated with drugs [4-6]. It has also been quietly noted that the rate of cancer incidence is positively correlated (or directly proportional) to technological advancements. It is obvious that Nanoscience and its associated fields such as nanotechnology and nanomedicine is actually in a relatively adolescence stage. This

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is, however, not to neglect the advances made to date. Providing an effective and a clear definition to the field of nanomedicine and creating a standardized approach to acquiring, sharing, and tracking relevant information on nanomedicine applications as well as products will give a better focus as to what is achievable in this field. Applications and products that are already in trials or used in humans are also briefly highlighted in this study.

1.1 Defining nanotechnology and nanomedicine

Diverse definitions as to what nanotechnology is perceived to be, have emerged. To put in perspective, "Nanoscience" is broadly viewed as the study of materials and their associated physical, biophysical, chemical and biochemical phenomena on the scale of ~1–100 nm (10-9 m). Though much of the biological processes occur on the nanoscale, we cannot say that Nanoscience has always existed. It is therefore expedient to clarify what this concept is in its entirety. Nanotechnology is a field that employs: technological tools and concepts to biology; engineering biological and chemical molecules toward acquiring functions that are different from natural processes; or manipulating biological systems via methods more precise than the conventional molecular biology, biochemical or synthetic chemical approaches. Nanotechnology has proved useful in a lot of scientific and technological breakthroughs and a few of such obvious strides include:

- Mechanical, heat and electrical energy derived from the heart beat and the tapping of fingers can be converted into electrical energy through nanotech materials, which can be used to recharge portable devices when built into fabrics of cloth.
- Nanomaterials have also been proven to stimulate the body into regenerating lost as well as damaged cells. This has been demonstrated in mice that were able to use paralyzed limbs again.
- Some of the major challenges of cancer treatment include off-target sites and the side-effects of treatments that can now be circumvented by the development of nanotech-coated therapeutics that has the ability to guide the drug to the target while ignoring healthy cells.
- Blades that can cut through stones and metal can now be made from steel containing nanotubes. This steel can last for a thousand years as evident in the popular Damascus steel
- Scientists can now build outfits for rescue operations on smooth surfaces of building structures without any external support. The inspiration for this was derived from geckos that possess nano-sized hairs that can fuse to smooth surfaces without falling off.
- The creation of an invisibility cloak, where nano-tube sheets can allow light to divert away from objects that "disappear" at extreme temperatures.
- Suits that are stab-resistant and bullet proof capable of stopping 9mm rounds are now made from carbon nanotubes. They are so resilient that they have to be cut into different shapes and sizes using a saw.
- Nanotechnology is also being employed in energy (including solar cells and -performance batteries), electronics with ultra-storage capacity [7], smart nutrients delivery, screening for contaminants [8], and single-atom transistors [9].

Even though the core definition of nanotechnology as well as nanomedicine continues to be an area of controversy without a universally agreed definition, we still have some acceptable descriptions as well as operational definitions that show what we are talking about. Etheridge et al., 2013 suggested that nanomedicine should be taken as the medical application of nanoscale or nanostructured materials that have been engineered to have unique medical effects based on their structure with at least one characteristic dimension up to 300 nm as against the common 100 nm, and tries to buttress this definition with the fact that many of the early definitions of nanotechnology took a cut-off around 100 nm. Giving the definition provided by the National Nanotechnology Initiative (NNI) as an instance, earlier definitions that established 300 nm as limit focused more on where quantum effects are most times restricted to structures on the order of one to tens of nanometers [10-12]. In addition to this defense, spectacular physiochemical behaviors sometimes show-up for nanomaterials with defining features exceeding 100 nm. For instance, the plasmon-resonance in 150 nm diameter gold nanoshells was under clinical investigation for cancer thermal therapy. Etheridge et al., 2013 concluded by saying that, although many applications of nanomedicine utilize feature sizes ≤100 nm, this cut-off rules out many applications with significant consequences hence, the choice of 300 nm to better encompass the unique physicochemical properties that is occurs on these scales.

2 The nature of nanomaterials

Engineering nanomaterials is the most rapidly growing branch of nanosciences, and their physicochemical

properties prove to be more advantageous than the bulk materials that have the same compositions. Nanomaterials exhibit distinct novel attributes that the same material at large size may not possess. Carbon lattices, metal oxides, micelles, liposomes, nanotubes and polymers, and many more examples of nanomaterials are made of diameter of less than 100 nm (0.1μm). Particle aggregates are capable of being broken down to even smaller particles through milling and/or dispersion which generates nanoscale particles rather than solvated materials [13]. The relatively increased surface area, the quantum effects (in some cases), and the nano-scale size are the three principal factors that give nanomaterials their distinct properties that distinguish them from the bulk materials. When mass is kept unchanged, miniaturizing nanoparticles will produce an increase in the total surface area of particles, generating additional physico-chemical properties that puts the further miniaturized nanoparticle ahead of the corresponding bulk [14-16]. For example, a particle with a diameter of 1000 nm should have 1015 number of particles per pound, and a surface area of 3×109mm^2 per pound. Comparatively, a particle with a diameter of 10 nm should have 1021 number of particles per pound, and a surface area of 3×1011 mm^2 per pound. Additionally, the translocation/pharmacokinetics and distribution of nanoparticles through the body is largely and unequivocally dependent on size. Hence, the adverse or unintended effects of miniaturized nanoparticles cannot actually be easily detected or predicted from the known toxicity of the same chemical constituent when it is still at the bulk size or at micro-size [14, 17, 18]. The main factor that makes nanomaterials suitable for pharmaceutical applications is their unique size. However, size, hydrophobicity, 3D shape, electronic configuration, photo/electro-chemistry amongst many other attributes are part of what makes us find nanomaterials useful and applicable to medicine. These attributes affect the absorption, distribution, metabolism and excretion (ADME) of engineered nanoparticles in vitro and in vivo. Taking out the size factor will limit the use of nanomaterials.

We can subdivide nanoparticles into two major groups:

- The labile nanoparticles. This group is majorly but not limited to organic products, and they are characterized by disintegration into many molecular components upon application. Such nanoparticles include liposomes, polymers, micelles, and nanoemulsions.
- The insoluble nanoparticles. This group is majorly but not limited to inorganic products, such as silica dioxide (SiO2), titanium dioxide (TiO2), fullerenes and quantum dots (QD) (e.g. carbon lattices, nanotubes, metal oxides). In essence, these remain intact.

The metabolic fate of nanoparticles in the body system to a great extent depends on the surface characteristics of any particular nanomaterials. The pharmacokinetic behaviors and biological effects associated with the different class of nanoparticles require serious investigation at cellular levels as there is no single universal "nanoparticle" that is fit for all kinds of needs. Each nanomaterial is therefore to be investigated and evaluated for the entire effects associated with the whole therapeutic process.

3 Application of nanotechnology in medicine

Its application in health and medicine is however, receiving more interest now, and focuses extensively on pharmaceuticals (figure 1) [19], cancer treatment [20], tissue regeneration [21], implantable materials and medical diagnosis and imaging [22, 23]. So much has also been emphasized about nanomedical applications, and it is ideal to point out that one of the major attributes of these materials is in the cytotoxic effects of certain engineered nanomaterials in destroying malignant cells/tumours. Wagner et al. summarized the findings of a 2005 study commissioned by the European Science and Technology Observatory (ETSO) [24], through which products that are in development and have gained approval through one stage or another have been clearly spotted (table 1). The study also took companies involved, economic potential and data on developing applications into consideration for some of the studies (table 2). There are five (5) basic stages that are involved from development to the use of nanomaterials in medicine. The stages are: basic nanoscience research, application development, preclinical study (animal models), clinical trials phases, and finally consumer commercial products.

3.1 Nano-science and the justification for nanomedicine

Two fields of medicine, regenerative medicine and personalized medicine, are currently seeking refuge in nanomedicine as an alternative. Medicine itself is at the mercy of diverse fields of science that have individual origins. We can actually say that medicine is a discipline that rides on the strength and knowledge of other scientific and

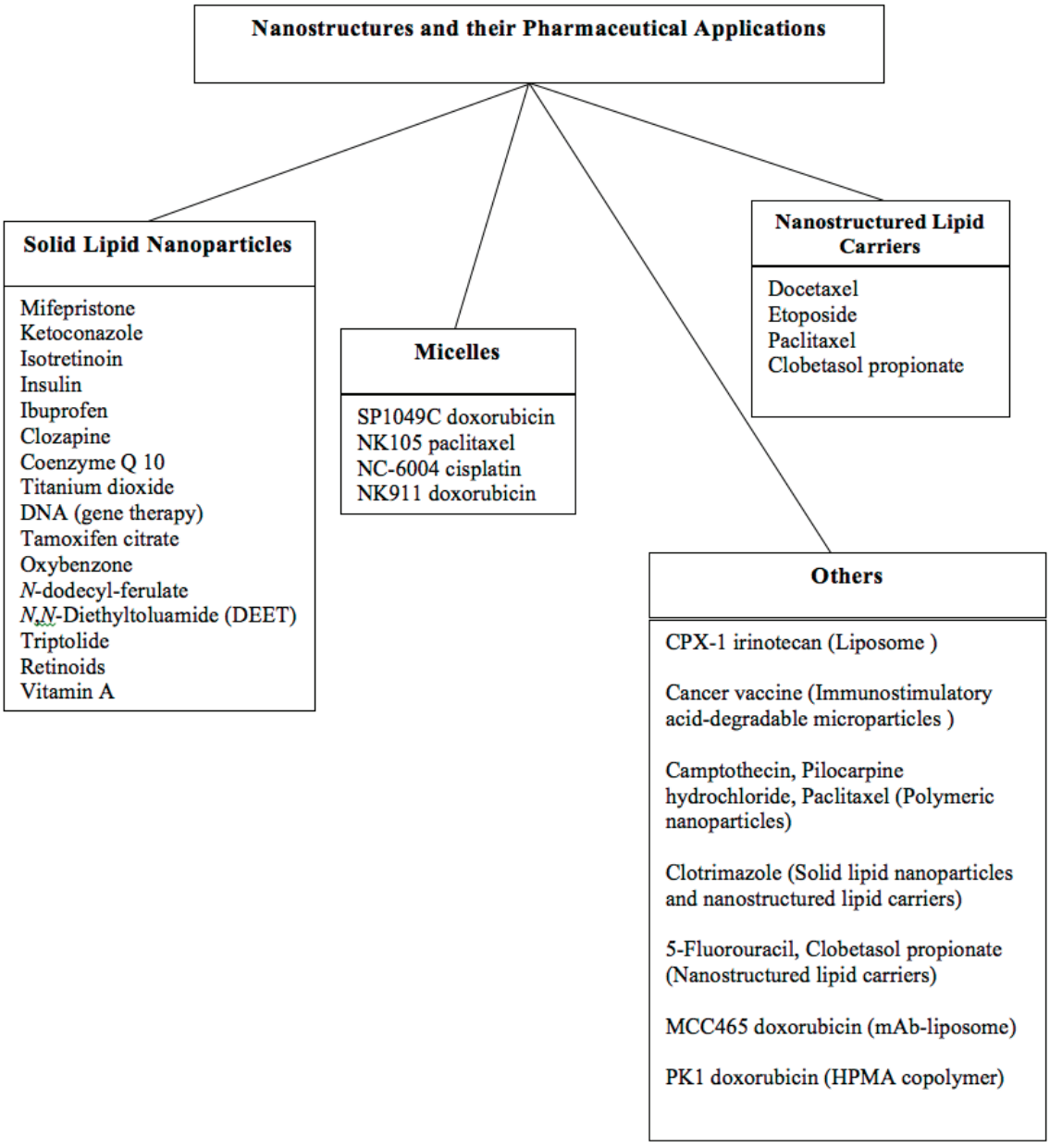

Figure 1: Nanomaterials and their application in pharmaceuticals

technological disciplines by harnessing the potentials in each of these fields of study. These scientific and technological fields include: the Natural sciences, Life sciences, Biomedicine, Molecular biology, Proteomics, Genomics, Biotechnology, Pharmacology, Nanotechnology, Nanomedicine, and many more fields. The evolution and convergence of the various related fields into nanomedicine is schematically depicted in figure 2. In the midst of varied descriptions of nanomedicine, the European Science Foundation in 2004 proposed nanomedicine to be the field of science and technology of diagnosing, treating and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body [54]. Since nanomaterials and the associated nanoscale devices are generally and typically comparable in size to DNA, viruses, subcellular organelles, proteins and gap junctions [55, 56], nanomedicine and other fields of medical research such as molecular medicine need to be strictly differentiated on the basis of phenomena at the nanoscale [57]. Defining Nanomedicine will not be a difficult one, as it is simply the application of nanotechnology to medicine. Summarily, nanomedicine is described as the science and technology of diagnosing, treating

Table 1: Products that are in development and have gained approval through one stage or another.

Product (s)/application (s)	Source/Company	Nanocomponent	Mechanism of target	Disease conditions	Broad Use
MBP-Y003, MBP-Y004, MBP-Y005 [25]	Mebiopharm Co., Ltd	loposome	transferrin	lymphoma	Lymphoma
SGT-53 [26, 27]	SynerGene therapeutics, Inc.	Liposomes	transferrin	Solid tumors	
Ontak [25, 28]	Seragen, Inc.	Protein Nanoparticle	IL-2 Protein	T- Lymphoma	
MCC-456 [29, 30]	Mitsubishi Tanabe Pharma Corp	Liposome	GAH Antibody	Stomach cancer	
MBP-426 [29, 31]	Mebiopharm Co., Ltd	Liposome	transferrin	Solid Tumors	Solid tumors
CALAA-01 [26, 32]	Calando Pharmaceuticals	Nanoparticle	transferrin	Solid tumors	
DM-CHOC-PEN [33]	DEKK-TEC, Inc.	Emulsion	Penetrate Blood-Brain-Barrier	Brain Neoplasms	
SapC-DOPS [34]	Bexion Pharmaceuticals, Inc.	Liposome	Saposin C	Solid tumors	
AS15 [27]	GlaxoSmithKline Biologicals	Liposome	dHER2 Antibody	Metastatic Breast Cancer	
PK2 [29, 35]	Pharmacia & Upjohn Inc.	Polymeric Nanoparticle	Galactose	Liver cancer	
Actinium-225-HuM195 [27]	National Cancer Institute	Nanoparticle	HuM195 Antibody	Leukemia	
Rexin-G, Reximmune-C [36]	Epeius Biotechnologies	Nanoparticles	Von Willebrand factor (Collagen-Binding)	Solid tumors	Solid Tumors
Aurimune (CYT-6091) [26, 37], Auritol (CYT-21001) [38]	CytImmune Sciences, Inc.	Colloid Gold	TNF-α	Solid tumors	
Targeted Emulsions	Kereos, Inc.	Emulsion	“Ligands”	In Vivo Imagine	
Opaxio [39, 40]	Cell therapeutics, Inc.	Polymeric Nanoparticles	Enzyme-Activated	Solid tumors	
thermoDox [41]	Celsion Corporation	Liposome	thermosensitive	Solid tumors	
Nanodots (Website, “Nanoco Technologies.”)	Nanoco Group PLC	Quantum Dot	Fluorescent Emission	In vivo imaging	In vivo imaging
FeraSpin (Website, “Miltenyi Biotec - FeraSpin™.”)	Miltenyi Biotec	Iron-Oxide Nanoparticle	Enhanced MRI Contrast	In vivo imaging	
Qdot Nanocrystals (Website, 2010, “QdotÂ® Nanocrystal Technology Overview.”)	Invitrogen Corpoaration	Quantum Dot	Fluorescent Emission	In vivo imaging	
eFluor Nanocrystals (Website, “eBiosciences: eFluor® Nanocrystals.”)	eBiosciences	Quantum Dot	Fluorescent Emission	In vivo imaging	

continued Table 1: Products that are in development and have gained approval through one stage or another.

Product (s)/application (s)	Source/Company	Nanocomponent	Mechanism of target	Disease conditions	Broad Use
TriLiteTM Nanocrystals (from: "Crystalplex Quantum Dots, Semiconductor Nanocrystals & Encoded Polystyrene Beads.")	Crystalplex Corporation	Quantum Dot	Fluorescent Emission	In vivo imaging	
NanoHC (Website, "DiagNano - Technology | DiagNano: Revolutionizing Diagnostics through Nanotechnology.")	DiagNano	Quantum Dot	Fluorescent Emission	In vivo imaging	
Clariscan (Website, "Veridex, LLC, a Johnson & Johnson company in vitro diagnostics oncology.")	Nycomed	Iron-Oxide Nanoparticle	Enhanced MRI Contrast	In vivo imaging	
NanoHC (Website, "DiagNano - Technology | DiagNano: Revolutionizing Diagnostics through Nanotechnology.")	DiagNano	Quantum Dot	Fluorescent Emission	In vivo imaging	
Resovist [42, 43], Supravist [44]	Schering	Iron-Oxide Nanoparticle	Enhanced MRI Contrast	In vivo imaging	
CellSearch®Epithelial Cell Kit (Website, "Veridex, LLC, a Johnson & Johnson company in vitro diagnostics oncology.")	Veridex LLC (Johnson & Johnson)	Iron-Oxide Nanoparticle	Magnetic Separation	In vivo imaging	
NanoDX (Website, "T2 Biosystems - NanoDx Nanoparticles.")	T2 Biosystems	Iron-Oxide Nanoparticle	Magnetic Separation	Cell Separation	In Vitro Cell Separation
NanoXray (45)	Nanobiotix	Proprietary Nanoparticles	X-Ray Induced Electron	Solid tumor	Solid tumor treatment
Endorem, Lumirem, Sinerem [42, 43]	Guebert	Iron-Oxide Nanoparticle	Enhanced MRI Contrast	Solid tumor	
Feridex IV, Gastromark Combidex (ferumoxtran-10) [42; 43]	Advanced Magnetics	Iron-Oxide Nanoparticle	Enhanced MRI Contrast	Solid tumor	
AuroShell ([46]	Nanospectra Biosciences	Gold nanoshell	IR Laser Heating	Solid tumor	Solid Tumor hyperthermia
NanoThern [45]	MagForce Nanotechnologies AG	Iron-Oxide Nanoparticle	AC Magnetic Heating	Solid tumor	
Targeted Nano-Therapeutics ("Technology - Aspen Medisys, LLC.")	Aspen medisys, LLC	Iron-Oxide Nanoparticle	AC Magnetic Heating	Solid tumor	

and preventing diseases towards ultimately improving human health. The applications of nanoparticles in nanomedicine actually stems from the enormous variety of attributes and unique characteristics of the nanoparticles under consideration. These characteristics are used in biomedical applications in the amplification of effects at the molecular level, by creating the required local concentrations of therapeutics. Currently, a lot of options are being considered in the use of nanomaterials in medicine, and some of them have received approval by various appropriate regulatory agencies such as the FDA. A few examples are briefly stated. Dendrimers capable of controlling drug delivery during gene transfection and also neutron-capture therapy are being investigated as potential therapeutics. The ability to track and monitor the therapeutic process such as tracing Quantum Dots (QDs) microscopi-

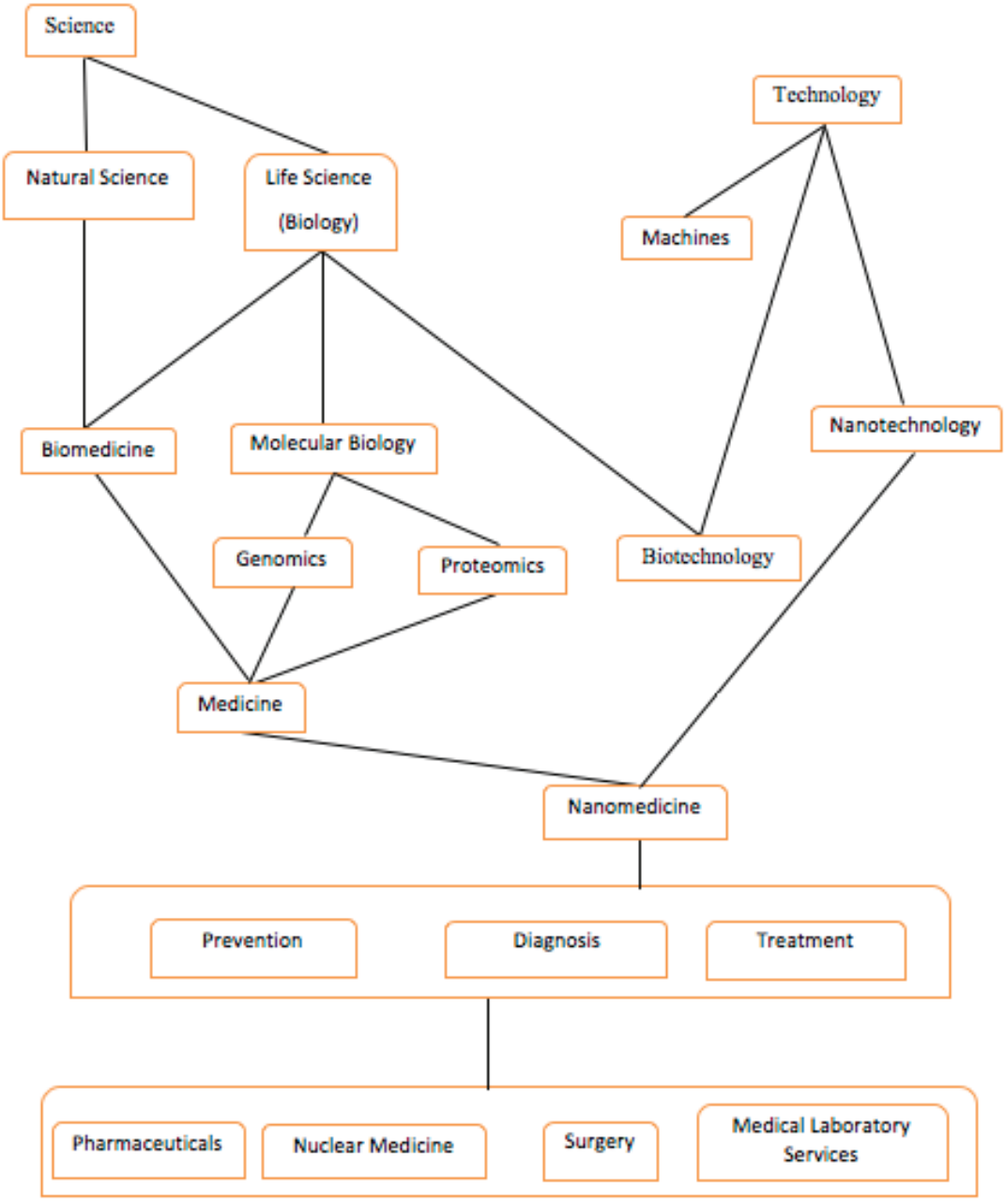

Figure 2: Evolution and convergence of some diverse related scientific and technological disciplines in nanomedicine.

cally as well as at ultrastructural levels via the principles of probes is largely instrumental in cellular dynamics. QD (most commonly Cd–Te, Zn–S, Cd–S, Pb–S and Cd–Se nanocrystals) probes are actually nanometer-sized (with 5–10 nm suggested to be more photo stable than the usual fluorophores) semi-conductors fortified with fluorescent property that make it suitable for biological imaging of molecules to which they are tagged [58-60]. Photoexcited TiO_2, capable of generating strong reactive oxygen species such as OH- and H_2O_2 is being investigated for the capability of suppressing the growth of tumor cells implanted in nude mice, potentiating for cancer therapy, including treatment of superficial cellular tumors in organs (such as trachea, urinary bladder, skin and oral cavity) not prone to damage by exposure to light. It is also vital to state at this point that the National Institute for Enviromental Health and Safety (NIEHS), the National Cancer Institute (NCI) led a National Nanotechnology Initiative, and the National Institute of Health, USA, have been trying to initiate, fund and foster preclinical toxicology studies to consider all the possible safety issues that could propel nanomedicine into clinical practice. The use of nanodrugs

Table 2: Nano-products approved for use, with dates.

Product(s)/application(s) plus year of approval	Source/Company	Nanocomponet Description	Broad use
Fresenius Polysulfone®, Helixone® (1998) ("NephroCare: Fresenius Polysulfone® Helixone® Dialysers.")	NephroCare	Nanoporous Membrane	Dialysis Filter
Filtek (2008) [47]	3M Company	Silica and Zrconium Nanoparticles	Bone substitute
OsSatura (2003) [48]	Isotis Orthobiologics US	Hydroxapatite Nanocrystals	
Vitoss (2003) [24]	orthovita	100 nm calcium-phosphate nanocrystals	
NanOss (2005) [45]	Angstrom medica, Inc.	Hydroxapatite Nanocrystals	
Ceram × Duo (2005) ("Ceram-X: Nano Ceramic Restorative.")	Dentspley	Ceramic Nanoparticles	
Ostim (2004) [49]	osartis	20 nm Hydroxapatite	
Alpha-bsm, Beta-bsm, Gamma-bsn, EquivaBone, CarriGen (2009) ("ETEX products are composed of a proprietary nanocrystalline calcium phosphate formulation that mimics the crystalline mineral structure of human bone.")	ETEX Corporation	Hydroxapatite Nanocrystals	
Acticoat® (2005) [50, 51]	Smith & Nephew, Inc	Anit-Microbial Nanosilver	Medical Dressing
ON-Q SilverSoaker/SilvaGardTM (2005) [50]	I-Flow Corporation/ AcryMed, Inc.	Anti-Microbial Nanosilver	Dental composite
Nano-Bond (2007) (Nano-Bond: Nano Particulate Reinforced Adhesive System, Pentron Clinical Technologies, LLC.)	Pentron® Clinical Technologies, LLC	"Nanoparticles"	
Premise (2003) [24]	Sybron Dental Specialties	"Nanoparticles"	
CellTracks® (2003) [24]	Immunicon Corporation	Magnetic Nanoparticles	Device Coating
NanoTite Implant (2008) (Website, "BIOMET 3i Implant Systems - NanoTite™ Implant - Introduction.")	Biomet	Calcium phosphate Nanocrystal Coating	
Stratus CS (2003) [48]	Dade Behring	Dendrimers	
EnSeal Laparoscopic vessel Fusion (2005) ("Nanotechnology and Medicine / Nanotechnology Medical Applications," The Project on Emerging Nanotechnologies)	Ethicon endo-Surgery, Inc.	Nanoparticle Coated Electrode	
NicAlert (2002) [24]	Nymox	Colloidal Gold	
TiMESH (2004) ("Nanotechnology and Medicine / Nanotechnology Medical Applications," The Project on Emerging Nanotechnologies)	GfE Medizintechnik GmbH	30 nm Titanium Coating	Tissue Scarfold
MyCareTM Assays (2008) (Website, "Saladax Biomedical | Product Pipeline Assays.")	Sladax Biomedical	"Nanoparticles"	In Vitro Assay
Verigene (2007) [52, 53]	Nanosphere, Inc	Colloidal Gold	
cellSearch® Epithelial Cell Kit (2004) (Website, "Veridex, LLC, a Johnson & Johnson company in vitro diagnostics oncology.")	Vendex, LLC (Johnson & Johnson)	Iron-Oxide Nanoparticles	

creates a dose differentiation between site of the target and the rest of the body, thereby maximising the therapeutic effects, while minimizing side-effects [62]. This is in contrast with the traditional methods used.

4 Nanomedicine in therapeutic medicine

The nanocarriers employed in nanomedicine are made of relatively safe materials, including but not limited to synthetic biodegradable polymers, polysaccharides and lipids. The essence of this is that, medicine tries as much as possible to stick closer to natural organic products as well as biodegradable natural products rather than inorganic and synthetic products. Various fields that play a part in therapeutic nanomedicine are depicted in Table 3.

Multifunctional nanoparticles play key roles in cancer therapeutics. Abraxane, one of the therapeutics approved by the FDA for the treatment of breast cancer, is a nano formulation made of paclitaxel (a very potent anticancer drug) conjugated to a nano-bead protein structure. The nano-bead conjugated protein moiety facilitates water solubility to enhance the elimination of the toxicity of cremaphor (the solvent vehicle) towards ultimately improving the therapeutic index. Likewise, nanoparticles (e.g TiO2) have been employed as optical filter carriers to protect the drug against light exposure damage and ultimately improve the photostability of pharmacologically active payload. There is also an improved hydrophilicity of TiO2, producing increased aqueous wettability and dissolution that disallows aggregation in the dispersion medium [62].

Carbon nanotubes (CNTs) are also a very important class of nanomaterials. Of the carbon nanotubes, the single-walled carbon nanotube (SWNT), usually linked covalently to the therapeutic drug of diagnostic sensor via ester disulfide bond, is of a very special interest because of its hydrophilic functionalized soluble nature. That grants it a wide application as a viable means of moving molecular cargo of different sizes and types across the highly selective cell membrane to the intended therapeutic target via various energy -dependent and/or –independent processes [63-65]. SWNTs are capable of binding to single/double stranded DNA, as well as peptide amino acids (PAA) [66-69]. When SWNTs enters the target compartment, they come in contact with the acidic environment of endosomes or lysosomes which has a reducing property, leading to the cleavage of the disulfide/ester bonds to selectively release the active therapeutic agent [70]. It has been demonstrated that nanoformulations of SWNTs conjugated to platinum (IV) could effectively deliver a lethal dose of the anti-cancer drug inside the malignant cancer cells [71]. Cationic functionalized CNTs (usually positively charged polyelectrolyte), are often employed in binding to DNA to facilitate specific target-delivery of functional DNA and siRNA in target gene expression studies and experiments. These Cationic functionalized CNTs nanotubes

Table 3: Diverse fields in therapeutic medicine

Nanomedicine in Therapeutic (treatment) Medicine			
Molecular Biology & Proteomics	**Pharmaceutics**	**Biomedicine, Biorobotic & Robotics**	**Biotechnology**
– Genetic therapy – Pharmacogenomics	– Drug delivery – Biopharmaceutics – Drug encapsulation – Smart drugs – Radiopharmaceutics – Antibacterial & antiviral nanoparticles – Photodynamic therapy – Fullerene-based pharmaceuticals – Target drug delivery	– Enzyme manipulation & control – Biological viral therapy – Artificial cells & liposomes – Polymeric micelles & polymersomes – Dynamic nanoplatform nanosome – MEMS surgical devices – Sensory aids (e.g artificial retina) – MEMS/Nanomaterials-based prosthetics – Diamond-based nanorobots	– Tissue engineering – Artificial organ – Stem cell and cloning – Virus-based hybrids

are intended to balance-out negative charge on the DNA, and this has helped generate lots of DNA sensors [72]. One of the vital procedures that must be well observed in putting a methodology into practice is the ability to track and monitor biological molecular processes in vivo and in vitro, and water-soluble semiconductor Quantum dots (QDs), such as cadmium selenide (CdSe) have proven to be effective in functioning in this capacity. This is achieved by capping CdSe with a shell of PEG, with a functional biotin surface.

Likewise, the administration of doxorubicin encapsulated in PEG-PE micelles improves doxorubicin accumulation and penetration in tumors, in comparison with what is obtainable without nanotechnological modification. Liposomes have been long used as viable transporters for therapeutics such as cisplatin, doxorubicin, paclitaxel, daunomycin and amphotericin, providing a practical approach for on-target and in time delivery aimed at reducing the risk of adverse effects as well as increasing bioavailability [73].

Doxil® and Abraxane are two examples of "first generation" nano-based drugs that have been fashioned for cancer chemotherapy, functioning in their capacity due to their physicochemical behavior on the nanoscale [74, 75]. Cancer cells can be effectively targeted due to the enhanced permeation and retention effect made feasible by this delivery system [76-78]. Approximately 5%–10% of all cancer drugs that are in clinical use today are nanodrugs. The solution to various infectious diseases has also been sought using nanotechnology, and they include endocrine/exocrine disorders, skin regeneration, cardiac/vascular disorders, corrective cochlear and retinal implants, degenerative disorders [10], increased efforts in sustained drug release in treating glaucoma [79, 80] improve heart function, and improved antimicrobials [81]. Most of the currently registered clinical trials (Table 4) in nanomedicine primarily focus on therapeutic approaches in managing malignant solid tumors.

4.1 Nanomedicine, stem cells, cancer, immune activation management, neurological diseases and regenerative medicine

Cancer is the major target of nanomedical research in the development of individualised diagnoses and treatments. Common anti-cancer agents have a poor biodistribution, and poor pharmacokinetics, creating adverse effects on healthy tissues [82]. By identifying disease biomarkers such as a protein, mutant gene, lipid, carbohydrate RNA, or small metabolites, targeted treatments can be designed using multifunctional nanoparticles that are able to detect and image tumours [83]. Some of the nanobased anti-cancer drugs currently used to treat various forms of cancer are reported in table 5. The broad mechanisms of the delivery of nano-therapeutic materials to cancerous tissue progresses generally via passive or active nanomedicine drug targeting. The passive targeting occurs due to the spontaneous drug accumulation in cancerous sites which possesses typically leaky vasculature. This ultimately provides enhanced permeation and retention effect [84]. Active targeting methods, on the other hand, exploits or takes advantage of the fact that, at the cellular level, a large number of pathological states may be identified by particularly displayed surface proteins that are absent in healthy cells. In some cases, these proteins are relatively over expressed when compared to healthy cells. This surface functionalization with ligands, which bind selectively to these proteins that are expressed on the surface of the unhealthy tissue, makes provisions for specific targeting of the nano-based therapeutics to the target diseased site [85]. The first sets of nanoparticles used for cancer treatment were biodegradable and biocompatible liposomes capable of carrying both hydrophobic and hydrophilic molecules [86]. They consist of a lipid bilayer surrounding an aqueous core, encapsulating the drug [83], highly endowed with the ability to permeate cell membranes easily to bind to DNA or RNA for transfection [86]. Dendrimers are also used for a range of therapeutics and diagnostics by carrying drugs either by encapsulation or conjugation in cancer, and in photodynamic therapy and hyperthermia therapies using AuNPs. Another landmark on the progress to curing cancer has been cancer stem cells (CSCs). They have similar properties to normal stem cells, but found within the tumour, therefore are tumorigenic, generating tumours through the stem cell processes. Targeting of CSCs within a tumour permits two types of targeting; active targeting that uses the binding of a specific target ligand to a specific receptor molecule, and passive targeting that relies on haemodynamic changes conventionally linked to the blood supply to tumours. Metastasis, tissue invasion, growth self-sufficiency, sustained angiogenesis, evasion of apoptosis, endless potential for replication and insensitivity to anti-growth signals, are all major hallmarks of cancer cells, and are hinged on a complex set of errors in the governing regulatory circuitry that defines homeostasis. In addition to their perfectly suited preferential transport of therapeutic agents to target cancer sites, nano- and micro-particulates are really ideal probes for study. Transport within and across body compartments and biological barriers differentiates healthy tissues and cancer cells [87]. This has been

Table 4: Some clinical trials in nanomedicine

Clinical trial Identifier	Area of application	Nanotherapeutic/nanodiagnostics	Main focus of study
NCT02104752	Schizophrenia; cognition; psychosis	Theracurmin formulation of curcumin nanoparticles	Curcumin as a Novel Treatment to Improve Cognitive Dysfunction in Schizophrenia
NCT02033447	Prostate cancer	Magnetic Nanoparticle injection	Magnetic Nanoparticle Thermoablation-Retention and Maintenance in the Prostate: A Phase 0 Study in Men (MAGNABLATEI)
NCT01167985	Endodontic treatment; irreversible pulpitis; infected pulp; etc	Device: IABN	A Clinical Study: the Antibacterial Effect of Insoluble Antibacterial Nanoparticles (IABN) Incorporated in Dental Materials for Root Canal Treatment
NCT02507596	Chronic periodontitis	Biological: nanocrystalline hydroxyapatite silica gel Biological: bone allograft Procedure: open flap debridement	Evaluation of Nano-crystalline Hydroxyapatite Silica Gel in Management of Periodontal Intrabony Defects
NCT01763710	Breast Cancer	Paclitaxel 80 mg/m2 Drug: Nab-paclitaxel 100 mg/m2 days 1, 8 and 15 Drug: Nab-paclitaxel 150 mg/m2 days 1, 8 and 15 Drug: Nab-paclitaxel 150 mg/m2 days 1 and 15	Neurotoxicity Characterization Study of Nab-paclitaxel Versus Conventional Paclitaxel in Metastatic Breast Cancer
NCT02549898	Migraine headache; migraine without aura	Drug: Feraheme Drug: cilostazol Other: USPIO MRI Other: BBI MRI	Investigation of Vascular Inflammation in Migraine Using Molecular Nano-imaging and Black Blood Imaging MRI
NCT01995799	Myocardial infarction; inflammation	Device: ferumoxytol-enhanced MRI	IRon Nanoparticle Enhanced MRI in the Assessment of Myocardial infarctioN (IRNMAN)
NCT00711230	HIV Infection	DermaVir: Placebo	Repeated DermaVir Immunizations in HIV-1 Infected Treatment-naïve Patients
NCT02479178	Urothelial carcinoma; cholangiocarcinoma; cervical cancer; squamous cell carcinoma of head and neck	Drug: BIND-014 (docetaxel nanoparticles for injectable suspension)	A Study of BIND-014 in Patients With Urothelial Carcinoma, Cholangiocarcinoma, Cervical Cancer and Squamous Cell Carcinoma of the Head and Neck (iNSITE2)
NCT01929785	Cardiac Transplant Failure	Application of In-House Developed Nanomedicine Technology for Diagnosis and Management of Post-Transplant Heart Allograft Patients	BIIR Gene to Manage Heart Allograft Patients
NCT00712530	HIV Infection	DermaVir|Drug: HAART	Single DermaVir Immunization in HIV-1 Infected Patients on HAART
NCT01463072	Male breast cancer; recurrent breast cancer; stage IV breast cancer; etc	Paclitaxel albumin-stabilized nanoparticle formulation	Paclitaxel Albumin-Stabilized Nanoparticle Formulation in Treating Older Patients With Locally Advanced or Metastatic Breast Cancer

continued Table 4: Some clinical trials in nanomedicine

Clinical trial Identifier	Area of application	Nanotherapeutic/nanodiagnostics	Main focus of study
NCT00918840	HIV Infection	DermaVir: Placebo|Drug: HAART	Antiretroviral-Sparing Concept With HIV-specific T Cell Precursors With High Proliferative Capacity (PHPC)
NCT02006108	Renal transplant rejection	Drug: Feraheme Other: MRI-GEHealthcare 3 Tesla magnet	Imaging Kidney Transplant Rejection Using Ferumoxytol-Enhanced Magnetic Resonance
NCT02755870	Healthy Volunteers - Male and Female	CNM-Au8|Other: Placebo	A Phase I SAD and MAD Clinical Trial of CNM-Au8 in Healthy Male and Female Volunteers
NCT02467673	Menopausal syndrome	Drug: micronized estradiol + progesteroneDrug: nanoparticulate estradiol + progesterone	Nanoparticulate Versus Micronized Steroids Delivery for Transdermal Hormone Replacement Therapy (Nanoparticle)

Table 5: Some of the nanobased anti-cancer drugs currently used to treat various forms of cancer

Drug	Nano-drug	Target/action
Tretinoin [102]	Loaded nanocapsules; Liposomes	Acute promyelitic leukaemia
Cisplatin [103]	DMPG-complexed, entrapped in liposomes	Melanomas
Mitoxantrone [103]	Cytostatic complex with lipophilic acid	Metastatic breast cancer, acute myeloid leukaemia, non-Hodgkin's lymphoma,acute lymphoblastic leukaemia
Daunomycin [104]	DaunoXome (liposome)	Leukaemia
Doxorubicin [103]	Doxil/ Caelyx-encapsulation in PEGylated liposome Myocet-non-PEGylated Liposome	Acute leukaemia, lymphoma, breast carcinoma, osteosarcoma, haematological malignancies, Kaposi's sarcoma Myocet-metastatic breast cancer in combination with cyclophosphamide
Paclitaxel/ Taxol [105]	Lipophilic prodrug paclitaxel oleate in sterically stabilized	Lung, ovarian, and breast cancer
Annamycin [103]	Liposome	Leukaemia, reticulosarcoma
Vincristine [106]	Liposome	Chemotherapy-nephroblastoma, lymphoma, lymphoblastic leukaemia
Hydroxyrubicin (lipophilic prodrug) [103]	Liposome	Leukaemia, reticulosarcoma

tested using variants of nanoparticles that can be manufactured in combinatory large sets, so that varying only one designed parameter at a time can explain the effects. This is mostly guided by a careful form of logic usually referred to as the Logic-Embedded Vectors "(LEV)" which forms ideal probes in application to nanoparticles for the determination of the laws of mass transport in and across tumors. This is to function as an imaging contrast enhancer. The full comprehension of the transport differentials expressed in cancer, often termed 'transport oncophysics' redefines a new hopeful frontier in oncology, producing greater efficacy in addition to reduced adverse effects. The Logic-Embedded Vectors "(LEV)" actually helps in boycotting the challenges of the barriers to transport of nanoparticles from the site of administration to the subcellular localization in target cells, foster-

ing specificity when the biosensors are incorporated. The specific and preferential targeting and locating of cancer sites by the administration of nanoparticles has greatly evolved as an attractive treatment strategy with a greater therapeutic index, topping the conventional formulations and designs of the same agents [87-91]. The first designed nanodrugs which were approved in the mid-Nineties were doxorubicin [92, 93] and liposomal encapsulated antifungals [94]. Another design employed the conjugation of albumin nanoparticles to Cremaphor®-free taxanes, and secured FDA approval in 2005 for the treatment of Breast cancer [95, 96]. The chaperoning effect of albumin is largely credited to the improved therapeutic index of taxane producing an enhanced extravasation in target tumors. It is recorded that Nanoparticles commands the market in excess of US$ 5.4 Billion per year [97]. Before nanotechnology emerged in medicine, radiopharmaceuticals [98], liposomal drug carriers [98, 99] antisense oligonucleotides, receptor-specific delivery of immunotherapy [100], and imaging contrast agents [101], have been used in the treatments of what nanoparticles have now proven better when properly employed. The 'first generation' nanotherapeutics have no particular biomolecular target recognition specificity, and they include the highly recognized clinically-approved liposomes as well as the albumin nanoparticles. Second-generation nanoparticles are the main focus of current research and are expected to perform other functions beyond the first generation. The main focus here is 'active targeting', that is the biomolecular targeting of cancer cell surface epitopes via nanoparticle surface-appended recognition moieties, such as peptides, antibodies or aptamers. This has been the focus for some years.

One major challenge in therapeutic medicine is tissue or organ rejection during transplant. Nanosized porous materials have been employed in immunoisolation of transplants to overcome this challenge. Via an encapsulation mechanism, semi-permeable membranes allow for the transport of oxygen and nutrients between the host environment and the transplant (cells), but blocks bigger immune cells such as monocytes and leukocytes from attacking the transplanted cells [107].

The Blood Brain Barrier (BBB), composed of brain endothelial cells, functions as the separation of the brain from the other parts of the systemic circulation, and being the main entry route of drugs into the CNS is a major limitation in the treatment of CNS diseases. This restriction of transport is via tight junctions, and through enzymes functioning as metabolic barriers [108]. All these factors are to be considered when designing nanocarriers. However, once molecules overcome the BBB to the cerebrum, they are extensively and quickly distributed throughout the brain, due to the high vascular density in the brain. For instance, modified liposomes have the record of being used in the management of neurodegenerative disorders. It is important to note that while liposomes without modification are usually incapable of crossing the BBB, PEGylated liposomes that are conjugated to monoclonal antibodies to glial fibrillary acidic protein (GFAP) would cross the BBB at the disease site [109]. There are also other methods of making liposomes transportable across BBB, including coupling it to transferring insulin receptors or mannose.

A very important field of medical research known as regenerative medicine describes the regeneration of lost or damaged tissue cells that are no longer functional. It focuses more on the regeneration of cells in the central nervous system (CNS). Diseases such as heart failure, pancreatic cells diseases, stroke, Parkinson's disease, Alzheimer's disease, paralysis due to spinal cord injuries and Multiple Sclerosis [110], can be restored in processes encompassed by regenerative medicine (Table 6). This includes regeneration of teeth, and musculoskeletal elements of tendon, bones, cartilages and ligaments [110]. PLGA and Nanosized titanium implants have been used extensively to bringing this to fruition [111].

5 Conclusion

Nanotechnology which involves engineering and utilizing materials at the nano-scale has shown a lot of promise in medicine and therapeutics. Nanomedicine, being a product of nanotechnology, is the process of using molecular tools and molecular knowledge of the human body for the purpose of diagnosing and treating illness. It may certainly change the ability to screen, diagnose and treat medical conditions that has hitherto posed as threats to human health. Medical conditions such as cancer, cardiovascular disease, endocrine diseases like diabetes, and other infections, may find cures through nanomedicine. Nanotechnology has already found useful applications in drug delivery e.g. delivery of chemotherapy drugs directly to cancer cells, drug release when sheer force is applied through sections of artery. Nanoparticles that deliver vaccine, sponge-like matrix delivering insulin, and nanoparticle enzymes that prevent reproduction of viruses are part of applications of nanotechnology in medicine. Other areas to which nanomedicine has been found useful include: nanotube-based biosensing devices that provide in vivo diagnostic testing capabilities, such as tracking

Table 6: Some of the nanobased neurological drugs currently used to treat neuronal diseases

Drug	Nano-drug	Target/action
5-chloro-7-iodo-8-hydroxyquinoline CQ [112]	Polymeric encapsulation	Cu/Zn chelator – Alzheimer's Disease
D-penicillamine (Cu(I) chelator) [112]	Nanoparticle encapsulation	Reverse metal induced Preceptiation
H0-1 gene [113]	Reducible poly (oligo-d-arginine) peptide	Protect brain cells from IR related injury, including stroke
Thioflavin-T [112]	Butylcyanoacrylate polymer encapsulation	Alzheimer's – detection of A_plaques
BCNU [114]	Magnetic nanoparticle with Fe3O4 core	Glioma
Mito-Q10 [115]	Attached to triphenyl phosphonium	Parkinson's disease
Doxorubicin [116]	PEGylated dendrimer with transferrin	G6 Glioma cells

electrolyte and blood glucose levels, synthetic biomaterials that mimic body tissues thereby enabling organ regeneration, faster and accurate infection and genetic testing tools that are less invasive than conventional methods. Some nanomedicine drug-delivery systems are already in use in anti-cancer drugs as already stated. Although nanomedicine has shown many possible breakthroughs in the management of diseases, it is necessary to employ some precautionary measures to protect the health and safety of patients, workers, the public and the environment. Areas that may require more research so as to avert possible future problems include the investigation of the toxicity profile of free nanoparticles which may be able to avoid the body's defenses and interfere with fundamental natural processes. Others include genetic alteration due to operation of some therapies at the chromosomal level which may be harmful to the unborn child, and issues of environmental and workplace safety as nanoparticles are often too small to be curtailed and may accumulate in water, air or plants, with unpredictable effects.

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