Nanotechnology & Nanomedicine



Hans Bluyssen, 23-11-2022

How Blood Swimming Robots Work



- Ability to enter cells and correct DNA or a deficiency.
- Repair cells, tissue, and even organs.
- Carry tiny cameras and be powered from the electrolytes in the blood.
- Break up blood clots or even kidney stones.

Nanotechnology

- Engineering and manufacturing at the scale of a nanometer or nanoscale (nanometer = 10⁻⁹ meter), a hundred-thousandth the width of a human hair.
- Examples of nano-substance are- Atom diameter 0.15 nm, diameter of double strand DNA 2 nm, and cell 10.000 nm.



Compared to Human Hair



A Human Hair is about 100,000nm wide

What is Nanoscale



Nanotechnology



Creation of functional devices in the nanometre range and the exploitation of the unique properties of these devices in various fields



patterns emerge. With the right arrangement of carbon atoms, a carbon nanotube can be hundreds of times stronger than steel, but six times lighter.

Where all the action is: the cell (10-30 um) !



Cells themselves (organelles) are very complex and efficient nano-machines.

Most areas of nanoscience aim to learn from biological nanosystems.

Watering flowers or flooding the neighborhood? treating atherosclerosis with lipid lowering drugs

arteriosclerosis:

- begins at the cell
- > *focal lesions* in the arteries
- leads to myocardial infarction and stroke



effects on plaques can save lives

effects on liver

Can endanger large

companies

arterial plaque

effects on immune system

muscles: can lead to cell death can endanger human life

!!!!!Solution: <u>Nanomedicine</u>

some lipid lowering drugs:

Nanomedicine



The application of nanotechnology to disease treatment, diagnosis, monitoring, control of biological systems

NANOTECHNOLOGY TOOL BOX

- NANOPORES
- NANOPARTICLES
 - NANOFIBERS
 - NANOELECTRONICS
 - NANOCANTILEVERS
 - NANORIBBONS
 - NANOCOMPOSITES

- NANOTUBES
- NANOCRYSTALS
- NANOARRAYS
- NANOPROBES
- NANOSHELLS
- NANOCOATINGS

• BUCKYBALLS

NANOTECHNOLOGY TOOL BOX

BUCKYBALLS hollow spherical molecules made up entirely of carbon

> Richard Buckminster ("Bucky") Fuller because buckyballs look like the buildings he designed

Nanoparticles



•⁸Re F, Moresco R, Masserini M. Nanoparticles for neuroimaging. Journal of Physics D: Applied Physics. 2012;45(7):073001.

The goal of nanomedicine is to develop safer and more effective therapeutic and diagnostic modalities



•McNeil SE. *J Leukoc Biol*, 2005. **78**(3): p. 585-94. •doi:10.1189/jlb.0205074

Nanomedicine

A vehicle for delivery of therapeutics into the body

Functionalized nanoparticles



- Small molecule drug compounds, DNA/genes, proteins, vaccines, etc.
- Administration routes to reach systemic circulation or infected organs and cells: oral, intravenous, inhalation, ocular, topical

Nanoparticle as delivery system for drugs or genes for tissue and cell





Functionalizednanoparticles

Nanoparticles and Drug delivery

Drug targeting by nanoparticles or nanocapsules offers the following enormous advantages:

- -Ingested vs injected
- -reduces dosage, ensures the pharmaceutical effects, and minimizes side-effects;
 -protects drugs against degradation and enhances drug stability.

Nanoparticles can penetrate through small capillaries and are taken up by cells, which allows efficient drug accumulation at target sites.

A sustained and controlled release of drugs at target sites over a period of days or even weeks is possible.



Nanoparticles and Drug delivery

- Nanoparticles with diameter less than 200nm are not screened out of circulation by liver and spleen.
- Nanotech based drug delivery is less toxic as well as inexpensive.

Nanoparticle use in Cancer Treatments

- Because of their small size, nanoparticles can pass through interstitial spaces between necrotic and quiescent cells.
- Tumor cells typically have larger interstitial spaces than healthy cells
- Particles collect in center bringing therapeutics to kill the tumor from inside out.



tumor cells





Injection site

A Drug Delivery Nanoparticle

A. Nanoparticles for drug delivery can be metal-, polymer-, or lipid-based. Below (left) an example of the latter, containing SiRNA encapsulated, and functionalized with a specific antibody. SiRNA can control often lethal inflammatory body responses, as shown in the microscopic images below (right)



Science 2008, Vol. 316, pp 627-630

Sick tissue treated with targeted nanoparticles

Dendrimers

Dendritic polymers = Dendrimers

Polyamidoamine (PAMAM) phosphorous-based, **Polylysine**

Highly branched structures – Molecular "hooks" – to attach Cell identification tags, fluorescent dyes, enzymes



ideal building blocks in nanochemistry for the creation of more complex three-dimensional structures.



The Michigan Nanotechnology Institute for Medicine and Biological Sciences



In Vivo Study: drug study in animals

- · Mice that received conventional drug: Free MTX
 - Lost hair (shutdown of protein synthesis)
 - Lost weight (general toxicity)
 - Non-necrotic tumors, no tumor reduction unless high dosis: drug ineffective
- · Mice that received drug in targeted Nanodevice
 - Retained hair
 - No weight loss (non-toxic)
 - Necrotic tumors, reduction in size with low dose of drug: drug effective

Targeting Works





Nanotechnology in Health Care

- Thermal ablation of cancer cells
 - Nanoshells have metallic outer layer and silica core
 - Selectively targeted to cancer cells
 - The nanoshells are heated with an external energy source killing the cancer cells



Thermal ablation of cancer cells assisted by nanoshells coated with metallic layer and an external energy source – *National Cancer Institute*

Diagnosis using Nanothermometers

Cancer cells appears to have a more elevated temperature than normal cells. Therefore, a local temperature mapping can be used to determine the spread of a tumor

A gold nanoparticle is functionalized with a PEG coating, which itself is assembled to a layer of smaller QD's. The emission properties of the nanoparticle change with temperature due to the stretching/contraction of the PEG



Thermal image of a healthy and cancerous breast

•Source: 9th European Congress of Thermology, Krakow, Poland



Angew. Chem. Int. Ed. 2005, Vol. 44, 7439 –7442

The goal of nanomedicine is to develop safer and more effective therapeutic and diagnostic modalities



•McNeil SE. *J Leukoc Biol*, 2005. **78**(3): p. 585-94. •doi:10.1189/jlb.0205074

What are Quantum Dots?

- Quantum dots are tiny particles or nanocrystals of a semiconducting material with diameters in the range of 2-10 nanometers (10-50 atoms).
- **Nanocrystals** can produce distinctive colors determined by the size of the particles: **Fluorescence**.

Enables long-term imaging experiments.



Excitation

Emission

widely exploited in the development of multicolor assays

Tuneability of Qdot® nanocrystals. Five different nanocrystal solutions are shown excited with the same long-wavelength UV lamp; the size of the nanocrystal determines the color.

Quantum Dot Bioconjugate

Qdot® bioconjugate is a generic term to describe Qdot® nanocrystals coupled to proteins, oligonucleotides, small molecules, etc., which are used to direct binding of the quantum dots to targets of interest. Laminin in a mouse kidney section was labeled with an anti-laminin primary antibody and visualized using greenfluorescent Qdot® 565 IgG. PECAM

(platelet/endothelial cell adhesion molecule; CD31) was labeled with an anti-PECAM-1 primary antibody and visualized using red-fluorescent Qdot® 655 IgG. Nuclei were stained with blue-fluorescent Hoechst 33342.



Targeting QD's for intracellular imaging

A. Using a drug-delivery-like mechanism, a targeted lipid-based nanoparticle (TNP) encapsulating QD's specifically 'attacks' a cell having the receptors that pair with its ligand coating. Upon ingestion and destruction of the TNP, the QD's are set free and accumulate on intracellular structures



Nano Letters 2008., Vol. 8, pp3887-3892



C. QD (red)intracellular uptake is enhanced when using the QDNC instead of the free QD's



D. Imaging of nucleus (blue) and cytoplasm (other) after 30 min (left) and 3 hours after uptake



Water soluble quantum dots to image sentinel lymph nodes which are used for diagnosing breast cancer.

Antibody-Modified Quantum dots for the sensitive imaging of the tumour tissue on a tumour-bearing mouse.



Nanotech in Disease Imaging & Therapeutic Monitoring

in vivo imaging system including the relationship between metastasis of cancer and the onset of angiogenesis and the efficiency of anticancer drugs.







The goal of nanomedicine is to develop safer and more effective therapeutic and diagnostic modalities



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Diagnosis

A. Detection of multiple biomarkers simultaneously

B. A specific phenotype of cancer cells has a particular combination of biomarkers on its membrane

C. Different phenotypes show different aggressiveness on their metastatic behavior



Source: www.cancernews.com

Multiplex Diagnosis

A. Four quantum dots of different diameter (i.e. different color) are respectively functionalized with four different antigens. Allowing for the distinction of two distinct phenotypes

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•Nature Protocols 2007. Vol. 2, pp. 1-15

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Lab-on-a-Chip

One of the more promising areas of nanofluidics is its potential for integration into microfluidic systems, i.e. <u>MicroTotal Analytical Systems</u> or <u>Lab-on-a-chip</u> structures





- •Credits: Mathies Lab, UC-Berkeley
- •Quake Lab, Stanford
- •Agilent, Inc.





Diagnostics – Biosensors

Novel Materials





Ultra-sensitive biosensor for the detection of bio-markers using bio-compatible ZnO nanowires.

ZnO nanowires

Lab-on-Chip in Health Care

- <u>Detection and Diagnosis</u>
- Lab on chips help detection and diagnosis of diseases more efficiently
- Nanowire and cantilever lab on chips help in early detection of cancer biomarkers



The microfluidic channel with nanowire sensor can detect the presence of altered genes associated with cancer – J. Heath, Cali. Insti. of Technology



The nanoscale cantilever detects the presence and concentration of various molecular expressions of a cancer cell – A. Majumdar, Univ. of Cal. at Berkeley

Nanomedicine in Atherosclerosis



Nanomedicine in Atherosclerosis



Macrophage-targeted nanomedicine for the diagnosis and treatment of atherosclerosis

Wei Chen¹, Maaike Schilperoort $\mathbb{D}^{2,3,4}$, Yihai Cao \mathbb{D}^5 , Jinjun Shi $\mathbb{D}^1 \boxtimes$, Ira Tabas $\mathbb{D}^{2,3,4} \boxtimes$ and Wei Tao $\mathbb{D}^1 \boxtimes$

NATURE REVIEWS | CARDIOLOGY

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Atherosclerosis & Macrophages



Non-invasive bioimaging technologies facilitate the visualization of high-risk atherosclerotic plaques with high spatiotemporal resolution.





Milestones in the development of nanoparticle-based imaging contrast agents and therapeutics for atherosclerosis diagnosis and treatment. NP, nanoparticle; USPIO, ultrasmall superparamagnetic iron oxide.

Studies on diagnosis		Studies on treatments
	1993	First nanocrystal drug (fenoglide) approved by FDA ¹⁶⁷
First MRI study of human atherosclerotic plaques by USPIO	1999	Atherosclerosis designated as an inflammatory disease ³
NPs (sinerem) ⁸⁶ USPIO NPs (sinerem) used to	2001	
assess macrophage-associated inflammatory burden by MRI ⁸⁷	2003	
ATHEROMA study: assessment of atorvastatin treatment effect on human carotid plaques by	2009	
USPIO-enhanced MRI ⁹²	2010	Light-activatable NPs for targeted macrophage ablation ¹⁴⁹
dalcetrapib assessed by PET–CT ¹⁰²	2011	
Dextran NPs for inflammation imaging by PET–MRI ⁷³	2013	(treatment with CER-001 HDL-like NPs) ^{194,195}
LOCATION trial: imaging atherosclerotic plaques with	2015	NANOM-FIM trial results reported (treatment with silica-gold NPs and plasmonic photothermal therapy) ^{151,193}
⁸⁹ Zr-labelled CER-001 HDL-like NPs ¹⁹⁷	2016	Targeted delivery of IL-10 by polymeric NPs for inflammation resolution ⁶⁷
USPIO NPs (feraheme) used to monitor carotid inflammation by MR1 ¹⁹⁸	2017	CANTOS trial results reported ³⁶
Imaging-assisted nanoimmuno-	2018	AEGIS-II trial initiation (treatment with CSL112 HDL-like NPs) ¹⁷⁸
treatment in multiple species ⁵⁸	2019	CIRT ¹³⁹ and COLCOT ³⁷ trial results reported
assess atherosclerotic plaque permeability by MRI ¹⁹⁸	2020	Initiation of clinical trials on treatment with methotrexate-loaded or paclitaxel-loaded LDL-like NPs ^{140,190}
Clinical study		
Preclinical study		

Imaging-assisted nanoimmunotherapy for atherosclerosis in multiple species

A <u>simvastatin-loaded high-density lipoprotein (S-HDL) nanotherapeutic</u> that we successfully applied in atherosclerosis mouse models to treat vessel wall inflammation.

Designed and implemented a high-pressure homogenization process, including innovative purification methods, to scale up S-HDL production, and generate the required amounts.

In this study, we report the escalation of a nanoimmunotherapy from mouse to large rabbit and porcine atherosclerosis models. Specifically, we integrated translational imaging readouts within the workflow to both analyze the nanoimmunotherapeutic's in vivo behavior and assess treatment response in larger animals.

We observed our nanoimmunotherapeutic's anti-inflammatory efficacy in mice as well as rabbits and pigs. Importantly, in the larger animal models, nanoimmunotherapeutically reduced inflammation halted plaque progression, underlining the approach's translatability and potential to acutely treat atherosclerosis.



Fig. 1. Nanoimmunotherapy production scale-up and evaluation in Apoe-/- mice.

Sci Transl Med. 2019 August 21; 11(506)



Fig. 2. S-HDL nanoimmunotherapy in vivo evaluation by non-invasive imaging in rabbits and pigs.

Sci Transl Med. 2019 August 21; 11(506)



Fig. 3. Imaging-guided S-HDL nanoimmunotherapy in rabbits and
pigs. PET-based readouts.Sci Transl Med. 2019 August 21; 11(506)



Fig. 4. Imaging-guided S-HDL nanoimmunotherapy in rabbits and pigs. MRI-based readouts Sci Transl Med. 2019 August 21; 11(506)

Targeted Interleukin-10 Nanotherapeutics Developed with a Microfluidic Chip Enhance Resolution of Inflammation in Advanced Atherosclerosis



Figure 1 Targeted anti-inflammatory NP design and application to resolution of inflammation in atherosclerotic plaques.

ACS Nano. 2016 May 24; 10(5): 5280–5292

Targeted Interleukin-10 Nanotherapeutics Developed with a Microfluidic Chip Enhance Resolution of Inflammation in Advanced Atherosclerosis

Here we present the development and efficacy investigations of controlled-release polymeric nanoparticles incorporating the anti-inflammatory cytokine interleukin 10 (IL-10) for targeted delivery to atherosclerotic plaques. Nanoparticles were nanoengineered via self-assembly of biodegradable polyester polymers by nanoprecipitation using a rapid micromixer chip capable of producing nanoparticles with retained IL-10 bioactivity post-exposure to organic solvent. A systematic combinatorial approach was taken to screen nanoparticles, resulting in an optimal bioactive formulation from in vitro and ex vivo studies. The most potent nanoparticle termed **Col-IV IL-10 NP22** significantly tempered acute inflammation in a self-limited peritonitis model and was shown to be more potent than native IL-10. Furthermore, the Col-IV IL-10 nanoparticles prevented vulnerable plaque formation by increasing fibrous cap thickness and decreasing necrotic cores in advanced lesions of high fat-fed LDLr-/- mice. These results demonstrate the efficacy and pro-resolving potential of this engineered nanoparticle for controlled delivery of the potent IL-10 cytokine for the treatment of atherosclerosis.



ACS Nano. 2016 May 24; 10(5): 5280–5292 **Figure 8** Col IV-IL-10 NPs increase subendothelial collagen in $Ldhr^{-/-}$ mice with established atherosclerosis.

Western diet for 12 wks



Decrease in cap thickness

ACS Nano. 2016 May 24; 10(5): 5280–5292

Figure 9 Col IV-IL-10 NPs decrease necrosis in $Ldh^{-/-}$ mice with established atherosclerosis.

Western diet for 12 wks



Decrease in necrotic core

ACS Nano. 2016 May 24; 10(5): 5280–5292

The Opportunity

<u>Problem</u>: For many cancers, response rates of patients treated surgically first, followed by chemotherapy and/or radiation are poor

- Surgery alone does not cure most patients of cancer
- > Following surgery, many patients present with metastatic disease

Need: Improve efficacy and safety, and minimize recurrent disease

- Targeting tumors
- > Limit exposure of healthy tissues and organs to cytotoxics

Solution: Use nanotechnology-based therapeutics, first

- > First treat patients medically to reduce tumors, use surgery only if needed
 - May lead to improved tumor regression, reduced side effects, and reduced recurrent disease



Design of CYT-6091 (Aurimune®):





Safe, Targeted Delivery: Size Matters



Too Large for Toxic Side Effects. CYT-6091 is small enough to safely travel through healthy blood vessels, but too large to pass through blood vessel walls into healthy tissues and organs, resulting in reduced toxicity.



Small Enough to Exit Tumor Vessels. All solid tumors are fueled by new, "leaky" blood vessels that have gaps in their walls. When CYT-6091 reaches these "leaky" vessels, the nanoparticles are small enough to pass through these walls into their target, the tumor.

Due to its engineered nanometer size and targeted capabilities, CYT-6091 is able to reduce toxicity and increase efficacy.



CYT-6091: Avoids Immune Recognition and Uptake

PEG bound to gold nanoparticles prevents uptake by the liver and spleen, major organs of the MPS, (black color is aggregated gold particles)

> Uncoated nanoparticles may be safe, but do not reach tumor target



Differential Uptake of CYT-6091 in Mouse Model

Electron micrographs comparing tumor and healthy tissue



Bar at bottom = 200 nm



Selective Induction of Vascular Leak by CYT-6091





Normal Vasculature No Vascular Leak

Albumin

Tumor Neovasculature Vascular Leak

CYT-6091 + Albumin CYTIMMUNE

Killing Tumors: CYT-6091 Pre-Clinical Mouse Data

Stealthy. PEG-Thiol bound to colloidal gold nanoparticles avoids immune detection by the MPS

Targeted. CYT-6091 delivers TNF to solid tumors:

- Passively by extravasating from the tumor vasculature
- > <u>Actively</u> by binding to TNF receptors on tumor endothelial cells

Accumulation. CYT-6091 accumulates TNF in TNF sensitive and insensitive tumors

- For TNF sensitive tumors:
 - One treatment induces potent anti-tumor responses at lower doses
- For TNF insensitive tumors:
 - One treatment induces transient anti-tumor response
 - Multiple doses causes cytostasis
 - Combination with doxorubicin is additive



Clinical Grade CYT-6091

Current production capacity scaled 10-fold from Phase I to Phase II

- > Solved manufacturing challenge for a nanomedicine
- Process is robust, reproducible and cost effective
- > 3-year shelf life as a freeze-dried product





CYT-6091 Phase I Trial: Clinical Observations

Safe, systemic delivery. <u>Delivered 1.2 mg of TNF with no dose</u> <u>limiting toxicity</u>

- No Hypotension, the dose-limiting toxicity associated with TNF use in man
- No Serious Adverse Events that were unexpected and related to treatment

Tumor targeted. Drug accumulation at tumor sites

> Gold particles seen in tumors but few if any in healthy tissues

Not Antigenic. No antibody response

> Titer checks after CYT-6091 treatments show no anti-TNF antibodies



Electron Micrographs* of a Patient's Biopsies

Patient diagnosed with inoperable breast cancer

- > Patient had no prior treatment; samples taken 24h after treatment
- > Drug accumulated in tumor, not in healthy breast tissue





Healthy Breast

Tumor

*Magnification = 20,000x



24

CYT-6091: An Ideal Cancer Nanomedicine

Designed to meet critical requirements for tumor targeted therapy

- Not picked-up by liver and spleen
- Fargets tumor endothelial cells
- > Manufacturing process robust, reproducible and cost-effective







A Diverse Pipeline of IO+ Therapeutics





Journal of Controlled Release Volume 330, 10 February 2021, Pages 372-397



Review article

Nanomedicines accessible in the market for clinical interventions

Vedant Gadekar, Yogeshwari Borade, Suraj Kannaujia, Kuldeep Rajpoot, Neelima Anup, Vishakha Tambe, Kiran Kalia , Rakesh K. Tekade 🙁 🖾

Fig. 1. Diagram illustrating various nanomedicines, which are currently in the market or under clinical trial.


Fig. 2. The trend of different NPs in the market.



Fig. 3. Classification of NPs-based drug delivery systems for clinical applications.



Fig. 4. Market trend, as well as the market size of the nanomedicines over the years.



Table 1 -

Datest Duratis Duratis Ovarian cancer, ALSe-clated Expon's Baronas Ben Vaue Laboratories, TT 1975 Dotarchicin Pepfade Ilposone Lipo Tosi Accident immus deficiency opdames (ALS)-claded stoper's across Materials Ben Vaue Laboratories, TT 1975 Datarchicin Nes pegfaded Ilposone Myoorf8 Materials Pract Planearchical Bia 2000 Datarchicin cluster Liposone Datarchicin Cluster Datarchicin Cluster Disorder State Datarchicin Cluster Disorder State Disorder Sta	Drug agent	Formulation type	Trade name	Clinical applications	Company	First introduced in the year
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DenorshinNon-pegifard lipomeMyoriffMetamate courtDama material matamaterial matamaterial matamaterial matamaterial matamaterial matamaterial 	Doxorubicin	Pegylated liposome	Lipo Dox®	Acquired immune deficiency syndrome (AIDS)-related Kaposi's sarcoma	Sun Pharma	2013
DescriptionUppose PariableDescriptionOutport of the series Arrange for series care Outport of the series care 	Doxorubicin	Non-pegylated liposome	Myocet®	Metastatic breast cancer	Enzon Pharmaceutical; Elan Pharmaceuticals	2000
heinstack instructions based NP possible based series possible instructions 	Daunorubicin citrate	Liposome	DaunoXom®	Acute myeloid leukemia	Gilead Sciences	1996
hinderson higher based formulation of transcore for hyperbase starsgy of	Paclitaxel	Albumin based NP's	Abraxane®	Breast cancer	Abraxis BioScience	2005
Dealekkin difface Protein based formulation Out & Out & Catanoous T-cell ymphona theory Biol 1999 (Synawise Constraints) Biol 1999 (Irinotecan	Liposome	Onivyde®	Metastatic adenocarcinoma	Merrimack Pharmaceuticals	2015
SyncholaseLiposomeDepoCyteBNeplastic meningitisBipder plantamentical properties Plantamentical properimital properimital properimital properimital properimital	Denileukin diftitox	Protein-based formulation	Ontak®	Cutaneous T-cell lymphoma therapy	Eisai	1999
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NameJurget directionsVersion (Second Second S	Leuprolide acetate	Sustained-release depot formulation	Eligard®	Prostate cancer	Tolmar Pharmaceuticals	2002
MaB Lipid containing NP's Abeleet® Invative fungal infection treatment Sputble 8 cons, LiC MaB Parenteral freeze-dried Amphotee® Syntemic fungal infection Caliant Biocreases 1995 Menyline sulfate Nanocrystal Rinalia LiA Arminoset® Press 2002 Menyline sulfate Nanocrystal Rinalia LiA Affention-deficit //spresstrivity disorder Pitzer 2002 Melyline information Nanocrystal Rinalia LiA Affention-deficit //spresstrivity disorder Nanocrystal 2009 mall interfering riboucieie Lipid complex siRNA Oppartro ¹⁰ Schenopkrenia Janseen Pharmacenticals 2018 Caliar disorders Lipid complex siRNA Oppartro ¹⁰ Hereditary transflyretin amyloidosis Alorjam Pharmacenticals 2019 Caliar disorders Lipid complex siRNA Oppartro ¹⁰ Hereditary transflyretin amyloidosis Alorjam Pharmacenticals 2001 Calid disorders Lipid complex siRNA Oppartro ¹⁰ Retails® Severe keratitis in dry eye patient Allegan 2002 Calidovacular diseases Nanocrystalline tablet Tricol® Primary hypercholesterolemia or mixed Abbot Laboratories 2001 Systemation Nanocrystalline tablet Tricol® Primary hyperch	Fungal infections Amphotericin B (AmB)	Lyophilised formulation	Fungizone®	_	Ben Venue Laboratories; E.R.	1966
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NaBParenteral freeze-driedAmphotes®Pangal infectionBen Venue Laboratories1996Neurological disordersNanocrystalAvinza®Prychortimulant Attention-deficit/typeractivity disorder Attention-deficit/typeractivity disorder MovartisPftzer Novartis2002MedbylipeuidateNanocrystalIvrega SchlaphreniaSchlaphrenia Attention-deficit/typeractivity disorder Attention-deficit/typeractivity disorderPftzer Physical-attention-deficit/typeractivity disorder Attention-deficit/typeractivity disorder <td>AmB</td> <td>Liposome</td> <td>AmBisome®</td> <td>Systemic fungal infection</td> <td>Gilead Sciences</td> <td>1997</td>	AmB	Liposome	AmBisome®	Systemic fungal infection	Gilead Sciences	1997
Neurological disorders Menubalise sufficient (Morphale sufficient (Morphale sufficient) Analysis (Moraris 2002 Meditylipenaidate Nanocrystal Ritalin LAR Affention-deficit/Apperacitivity disorder Paliperdological hydrochloride (MIRA) Colar diorders Wettgorffa (MIRA) Manocrystalline tablet Tricor [®] Trigide [®] Wettgorffa (MIRA) Colar diorders Wettgorffa (MIRA) MIRA	AmB	Parenteral freeze-dried	Amphotec [®]	Fungal infection	Ben Venue Laboratories	1996
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VerteportinLipsomeVisudyne®Choroidal neovascularizationOLT Phototherapeutics2001CyclosportinNanoemulsionRestais®Severe kentitis in dry eye patientAllergan2002Cardiovascular diseasesNanocrystalline tabletTricor®Primary hypercholesterolemia or mixedAbbott Laboratories2004FenofibrateNanocrystalline tabletTrigilde®Primary hypercholesterolemia or mixedAbbott Laboratories2005Blood disordersSemi-synthetic iron oxideFeraheme™Anemia related to chronic kidney diseaseAMAG Pharmaceuticals2009NPaInon NP'sInjectafer®Iron deficiency anemiaVifor Int.2013oxytydroxideIron NP'sInjectafer®Iron deficiency anemiaPharmacosmos2010unbranched carbohydrateIron NP'sMonofer®Iron deficiency anemiaPharmacosmos2010whenched carbohydrateFolymer protein conjugateMircera®CKD associated anemiaHoffman-LaRoche2007(MCO)-opotin betaRecombinant anti-hemophilicFolymer-protein conjugateNeulaata®Febrile neutropeniaAmgen2002Carandocyte-coloryFeylated NP'sPegasys®Hepatitis B and C therapyGenemtech biotechnology2002Unre diseaseNanocrystalOrtims®Sengenytaline, cell migration, cell migration, and boneOrthovita2003where roaliesNanocrystalVitoss®Bone growth and bone formationOrthovita2004unbrancher coligical miresNanocrystal	Ocular disorders					
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	Dermatological diseases Silver	Silver NP's	PolyMem®	Chronic diabetic foot ulcers	Ferris MFG. Corp. (Burr	-

Fig. 5. Summary of marketed products available for treating several illnesses.



Fig. 6. Summary of various nanoplatforms available in the market.



Table 4

Some essential nanotechnology-based formulations under clinical trials for the treatment of various illnesses.

Drug agent	Product name	Formulation type	Inventor/Company	Outcome	Clinical Status	References
Cancers Cisplatin Doxorubicin	LiPlaCis Thermodox	Liposome Lyso- thermosensitive liposomes	LiPlasome Pharma Celsion Corporation, USA	Stimuli-responsive targeted delivery for solid tumors Targeted delivery for hepatocellular carcinoma, refractory solid tumors, liver tumors, breast cancer	Phase I Phase I, II, and III	[196] [119]
siRNA	TKM- 080301	Lipid NPs	Arbutus Biopharm	Treatment of hepatocellular carcinoma and has completed phase I/II trials.	Completed phase I/II trials	[68]
Paclitaxel	Paclical	Polymeric micelles	Oasmia Pharmaceutical AB	Ovarian cancer	Completed phase III	[197]
Docetaxel	BIND-014	polymeric micelles	BIND Therapeutics	Targeted therapy for various cancers like prostate, non- small cell lung, cervical, metastatic, KRAS positive lung cancer	Completed phase II trial	[198]
Paclitaxel	NK105	polymeric micelles	Nippon Kayaku	Better tolerability an efficacy in gastric cancer	Completed phase	[199]
Rapamyein	ABI-009	albumin-based NPs	Aadi with Celgene	Increase safety margin for the treatment of various cancers like neuroendocrine tumors, bladder cancer, colorectal cancer, perivascular epithelioid cell carcinoma, and glioblastoma	Phase I and II trials	[200]
Hafnium oxide	NBTXR3	Crystalline NPs	Nanobiotix	Enhanced tumor destruction and for an indication of locally advanced squamous cell carcinoma, prostate, rectum, liver, head and neck cancer	Phase I and II trials	[201]
Liver diseases siRNA	ND-L02-	Lipid NPs	Nitto Denko/Bristol-	Targeted therapy for advanced liver fibrosis	completed lb/II	[202 203]
siRNA	s0201 ARB- 001467	Lipid NPs	Myers Squibb Arbutus (Tekmira) Pharmaceuticals	Hepatitis B	clinical trial Completed clinical phase II studies	[204]
Inflammatory disord Pegsiticase and rapamycin	lers SEL-212	Polymeric NPs	Selecta Biosciences	Improved management of uric acid level in case of gout	Phase II	[205,206]
Imaging application Gadolinium	s AGuIX	Inorganic NPs	NH TherAguix	MRI contrast agent for brain metastases and gynecologic	Phase I study	[207]
Indocyanine	ONM-100	polymeric micelles	OncoNano Medicine	Imaging agent in intraoperative cancer	Phase I	[208]
Cy5(organic dye) and radiolabel ¹²⁴ I	Cornell dots	Surface functionalized silica NPs	Ulrich Wiesner	Hybrid PET-optical tumor imaging of various cancer like brain, breast, colorectal, head and neck cancers	Phase I/II study	[209]
Vaccines mRNA-1944	Lipid NPs	Chikungunya	Moderna	Capable of eliciting chikungunya virus neutralizing antibodies	Phase I	[210]

