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Sviluppo di nano-farmaci antitumorali a rilascio controllato nell'era della medicina di precisione

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CNR NANOTEC – Institute of Nanotechnology

EUROPEAN BIOTECH WEEK
INNOVATION IS IN OUR GENES

FEDERCHIMICA ASSOBIOTEC
Associazione nazionale per lo sviluppo delle biotecnologie

PART OF GLOBAL BIOTECH WEEK

Coordinated by
CVBF
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General Assembly led by
National Research Council of Italy

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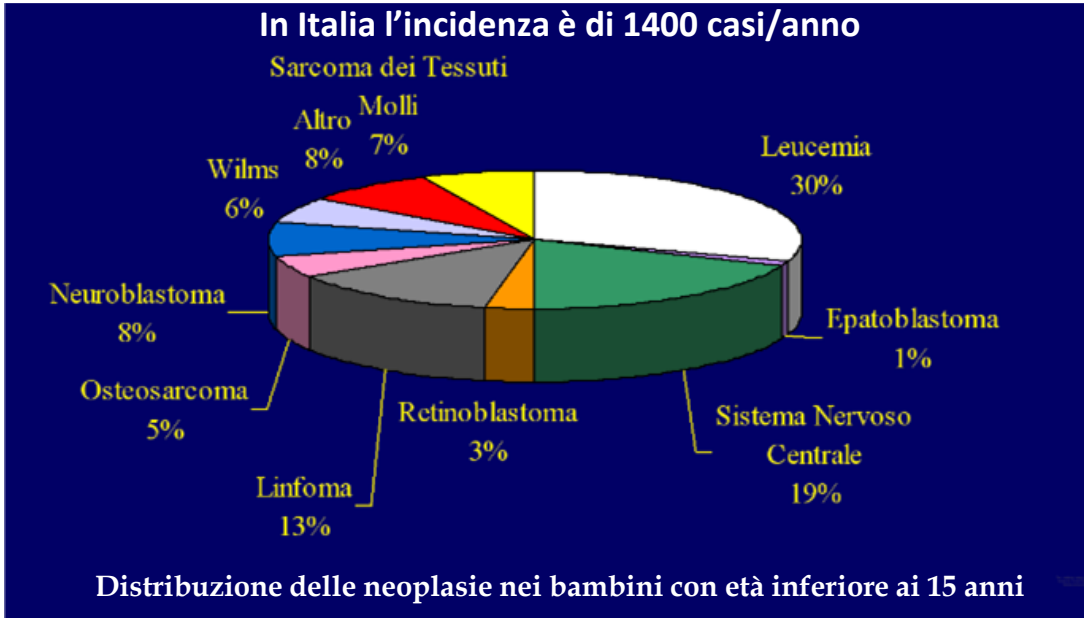
Sviluppo di nano-farmaci antitumorali a rilascio controllato nell'era della medicina di precisione

Pediatric tumors represent the most common cause of death in the children. The gold standard therapeutic options for cancers in children, as in adults, is chemotherapy for hematological cancers and tumor resection followed by radio- and chemotherapy for solid cancers, but with discouraging therapeutic results



Innovative therapies, such as nanocarriers that are capable to improve outcomes and lessen toxicities from current therapies are explored

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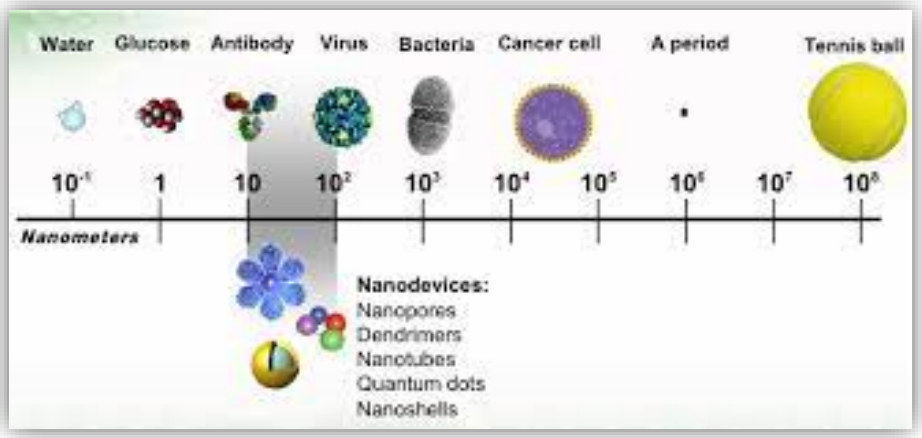

- Nanoparticles are sub-nano sized colloidal structures composed of natural or synthetic polymers

- Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000 nm

- Biomolecules and/or drugs are dissolved, entrapped, encapsuled or attached to a nanoparticles matrix

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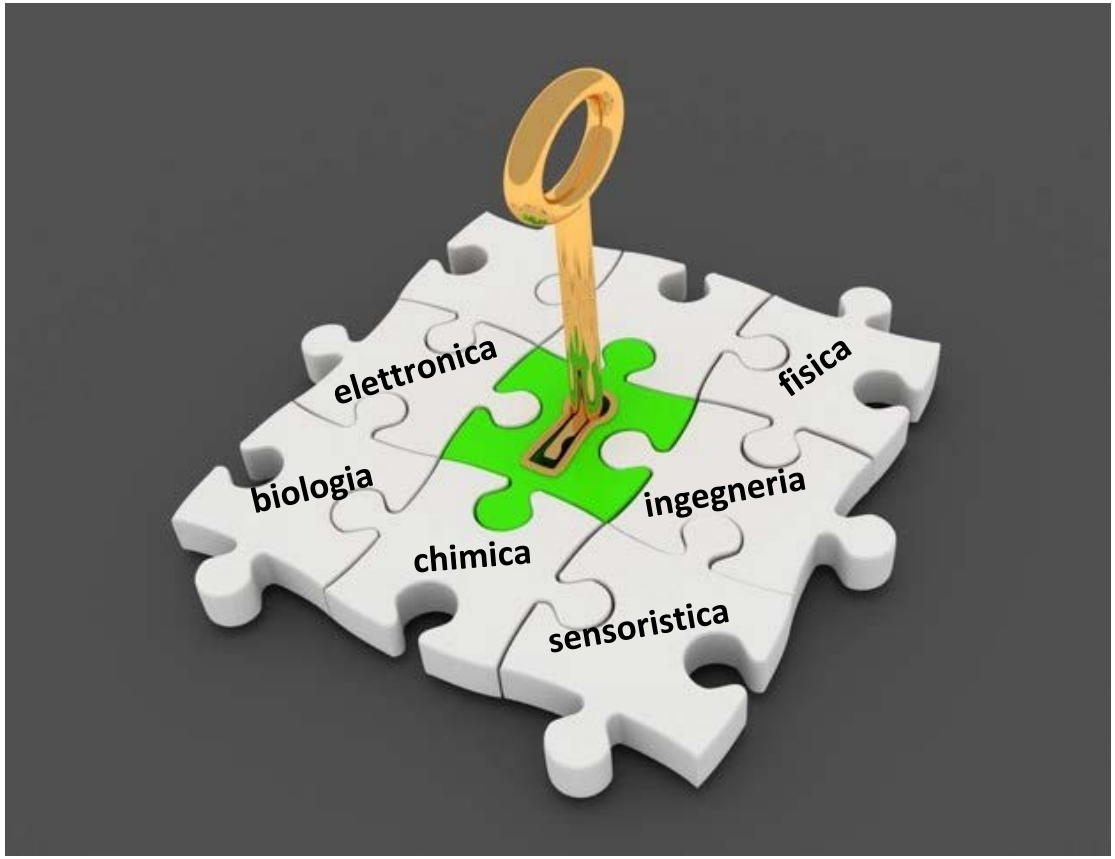
Nanoscienze



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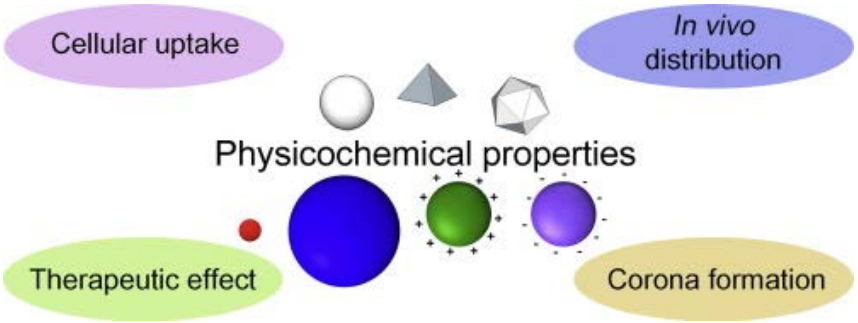
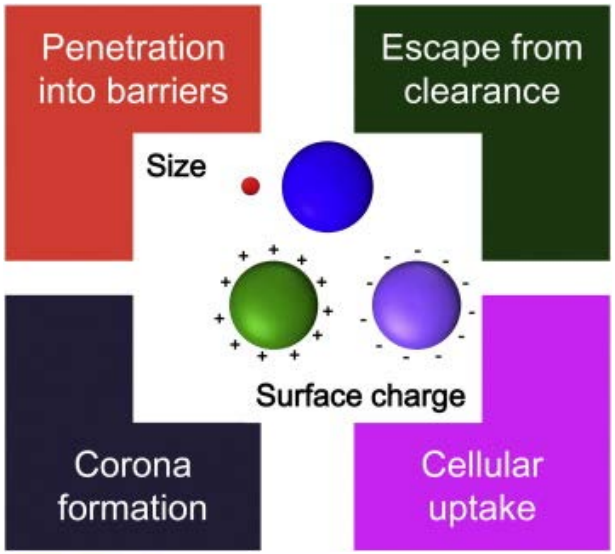
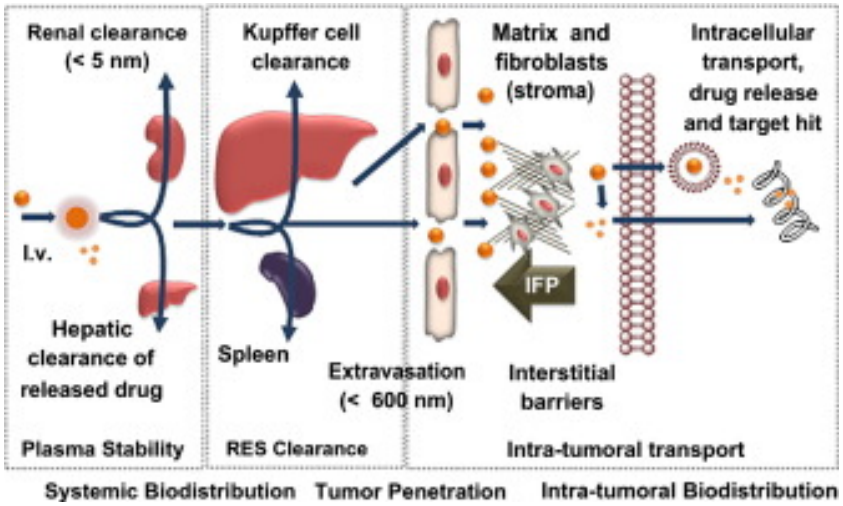
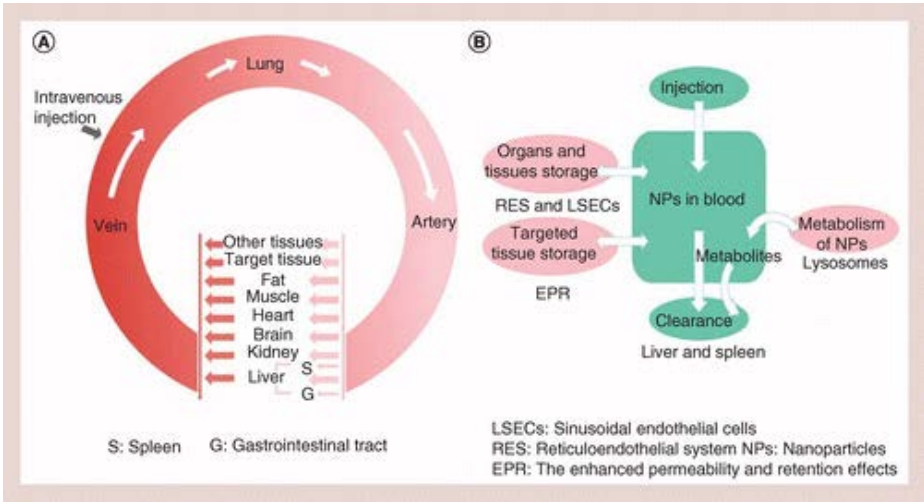
Proprietà chimico-fisiche dei sistemi di delivery









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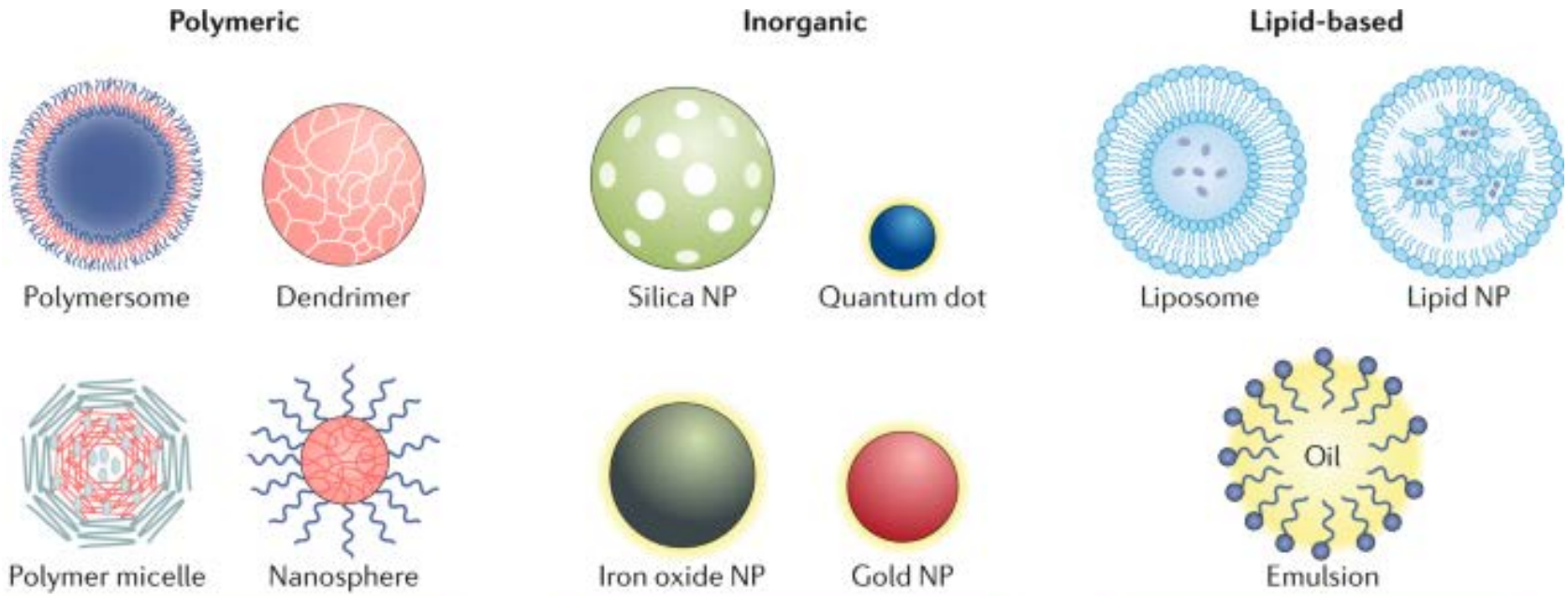
Sistemi per il rilascio controllato di farmaci



- Precise control of particle characteristics
- Payload flexibility for hydrophilic and hydrophobic cargo
- Easy surface modification
- Possibility for aggregation and toxicity

- Unique electrical, magnetic and optical properties
- Variability in size, structure and geometry
- Well suited for theranostic applications
- Toxicity and solubility limitations

- Formulation simplicity with a range of physicochemical properties
- High bioavailability
- Payload flexibility
- Low encapsulation efficiency

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Nature Reviews Drug Discovery 2021

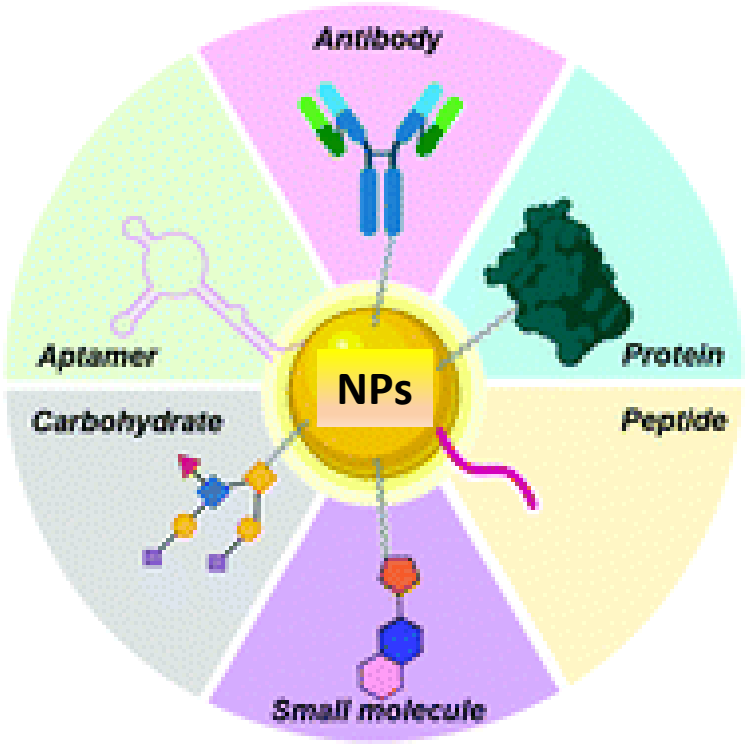
Targeting

La scelta del bersaglio da usare nel *drug targeting* dipende:

- Tipo di cellule
- Tipo di farmaco

Targeting passivo → Effetto EPR

Targeting attivo → Ligandi specifici: anticorpi, frammenti anticorpali aptameri, zuccheri, e small molecules



I due metodi di direzionamento possono essere **combinati** per aumentare la capacità di discriminazione del sistema tra tessuti normali e patologici

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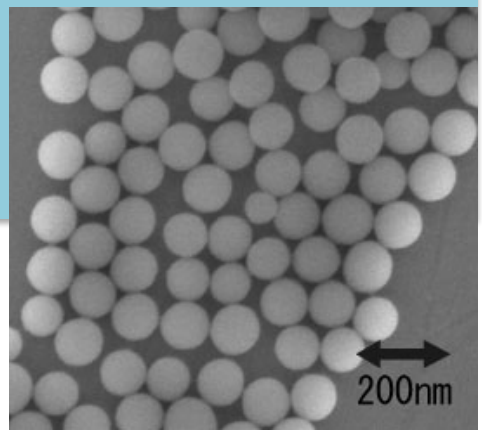
Features:

- Passive and active drug targeting in parenteral administration
- Control and sustain release of the drug
- Site-specific targeting
- Used various routes of administration including oral, nasal, parenteral, intra-ocular, etc.
- High drug loading



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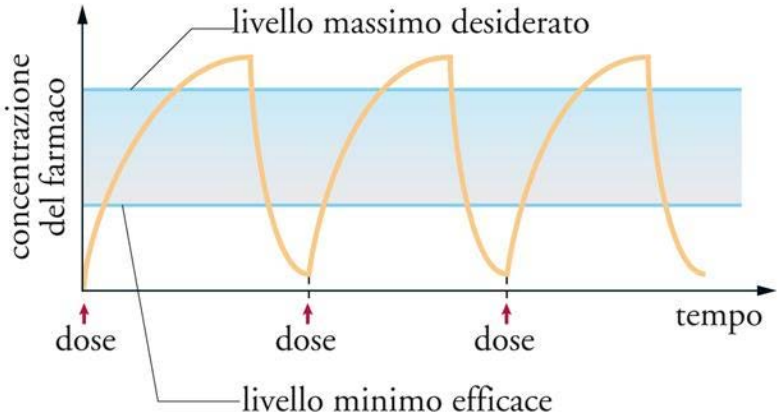
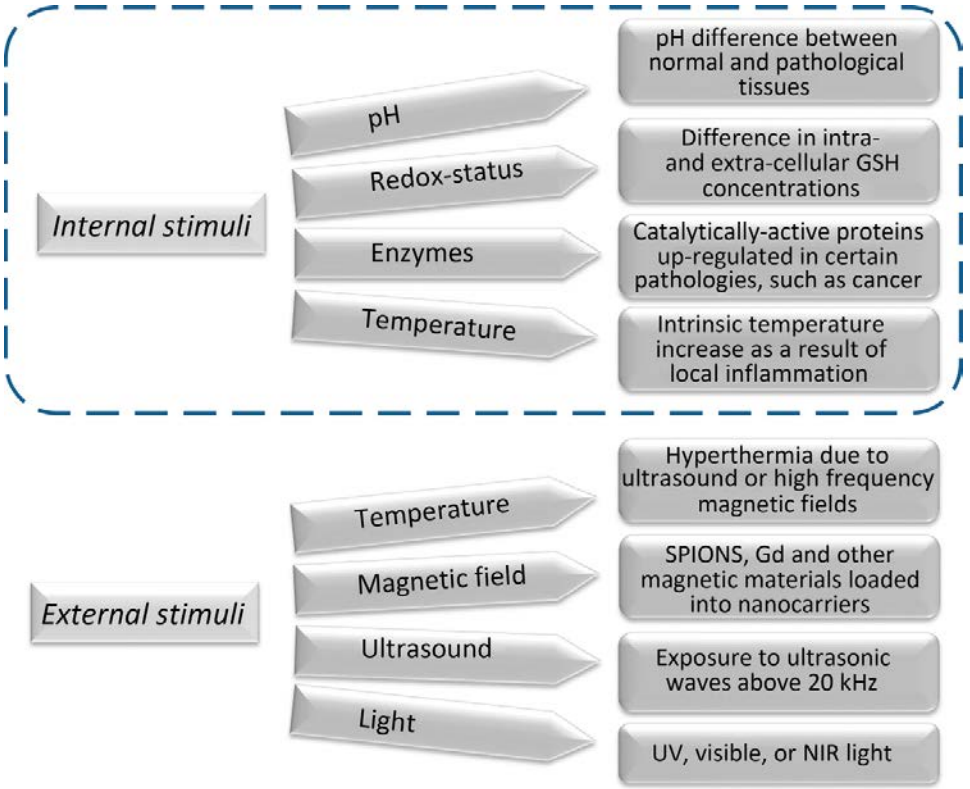
Come controllare il rilascio?





Controlled release of drugs is achieved by the release of encapsulated drugs through surface or bulk erosion, diffusion, or triggered by the external environment, such as changes in pH, light, temperature or by the presence of analytes.

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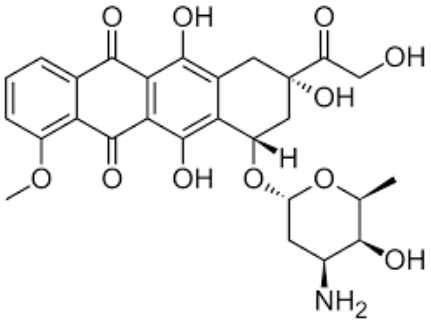
Nanoformulazioni attualmente in uso in clinica

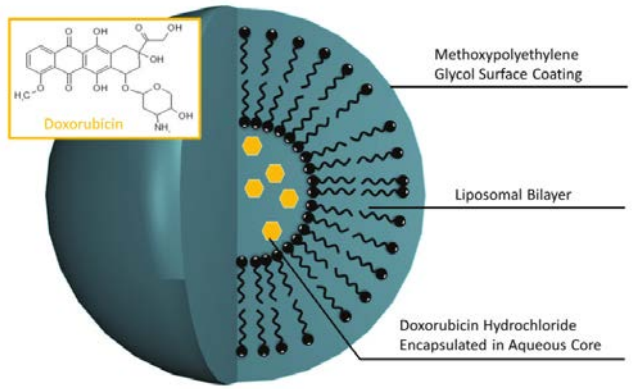
Name	Company	Material	Drug	Disease/s	Approved
Doxil/Caelyx	Janssen	Liposome	Doxorubicin	Kaposi sarcoma Ovarian cáncer Multiple myeloma	1995 2005 2008
DaunoXome	Galen Pharma	Liposome	Daunorubicin	Kaposi sarcoma	1996
DepoCyt	Sigma Tau	Liposome	Cytarabine	Lymphomatous meningitis	1999
Myocet	Elan Pharma	Liposome	Doxorubicin	Breast cancer	2000
Lipodox (generic Doxil)		Liposome	Doxorubicin	Same as Doxil	2013
Marqibo	Onco TCS	Liposome	Vincristine	Acute Lymphoma Leukemia	2012
Onivyde	Merrimack	Liposome	Irinotecan	Pancreatic cancer	2015
Vyxeos	Jazz Pharma	Liposome	Daunorubin Cytarabine	Acute Myeloid leukemia	2017
Oncaspar	Enzon Pharma	Polymer	.Aspargase	Acute Lymphoblatic eukemia	1994
Copaxone	Teva	Polymer	Glatiramer acetate (synthetic protein)	Multiple sclerosis	1996
Eligard	Tolmar	Polymer	Leuprolide acetate	Prostate cancer	2002
Plegridy	Biogen	Polymer	PEG-Interferon beta-1a	Multiple sclerosis	2014
Glatopa (Generic Copaxone)	Novartis	Polymer	Glatiramer acetate (synthetic protein)	Multiple sclerosis	2015
Ontak	Cisai Inc	protein	Denileukin diftitox (Synthetic protein)	Cutaneous T-cell lymphoma	1999
Abraxane	Celgene	protein	Paclitaxel	Breast Cancer NSCLC Pancreatic cancer	2005 2012 2013
Invega Sustenna	Janssen	nanocrystals	Paliperidone Palmitate	Schizophrenia	2009
Nanotherm	MagForce	Inorganic	Iron oxide	Glioblastoma	2010
Onpattro	Alnylam Pharmaceuticals	Lipid/Liposome	Patisiran (ALN-TTR02)	hATTR Amyloidosis	2018
ThermoDox	Celsion	Liposome,	Doxorubicin	Hepatocellular carcinoma	Phase III completed ClinicalTrials.gov identifier#NCT00617981
Paclical	Oasmia Pharma	Polymer	Paclitaxel, Doxil	Ovarian cancer	Phase III completed. ClinicalTrials. gov identifier# NCT00989131
NK-105	Nippon Kayaku	Polymer	Paclitaxel	Breast cancer	Phase III completed ClinicalTrials.gov identifier# NCT01644890

Nanoformulazioni attualmente in uso in clinica

The clinically used liposomal formulation (*ie*, Doxil®) is known to reduce the cardiotoxicity that is commonly associated with free doxorubicin (DOX) solution, but it does not efficiently enter cancer cells and release the loaded DOX intracellularly

As a result, it does not demonstrate improved efficacy compared to free DOX in solution despite its increased half-life and tumor accumulation and reduced cardiotoxicity





In the application of nanotechnology to drug delivery, the design of nanocarriers must be placed in the context of the pharmacology of the delivered drugs, that is, to deliver the drugs to the *right* site at the *right* time and the *right* levels (*3Rs*).

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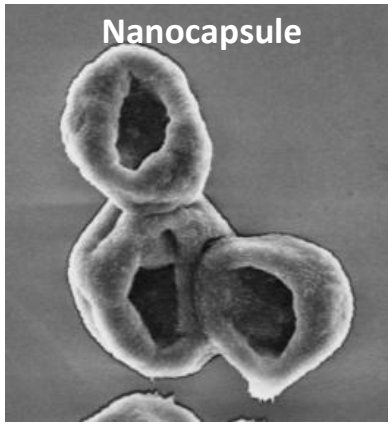

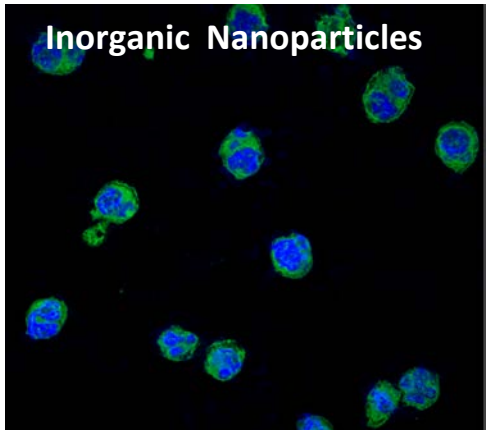

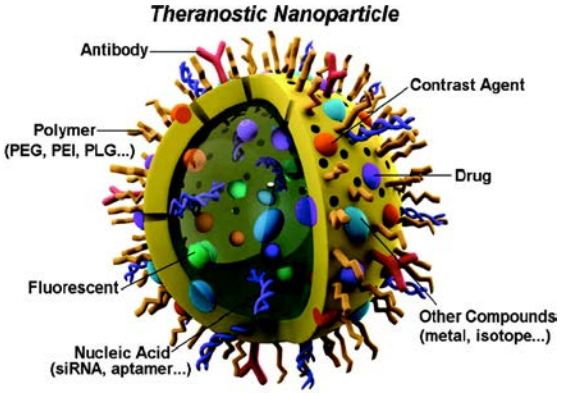

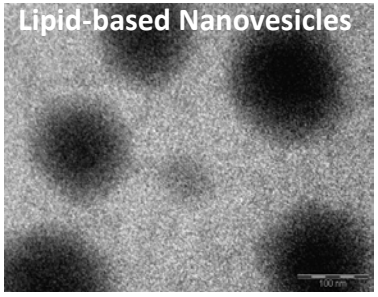

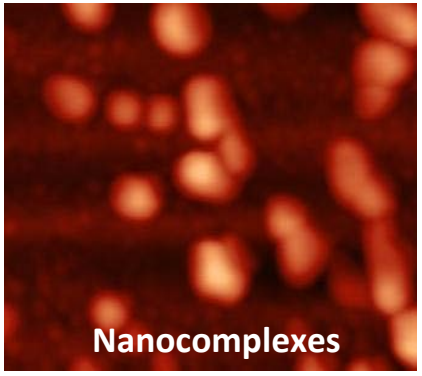

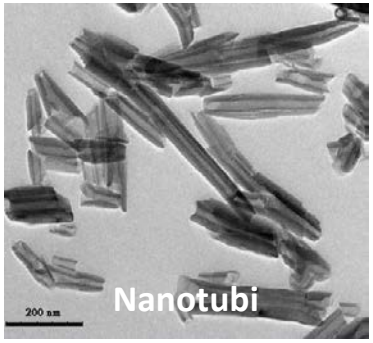

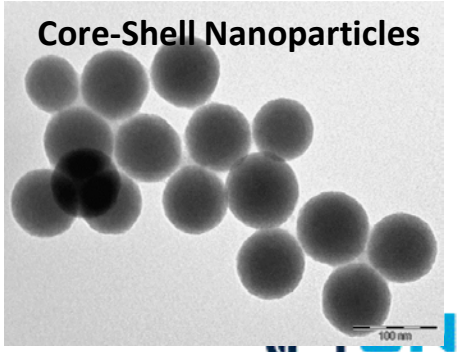

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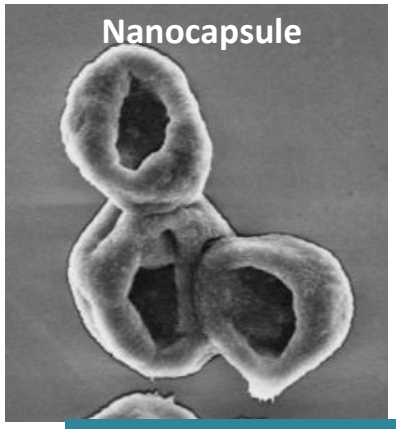
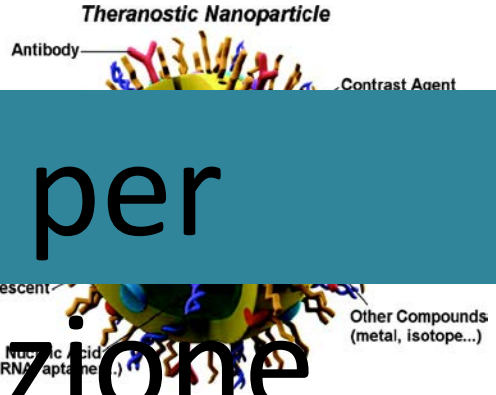
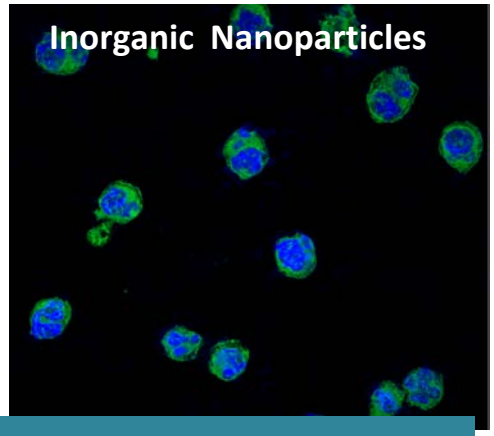
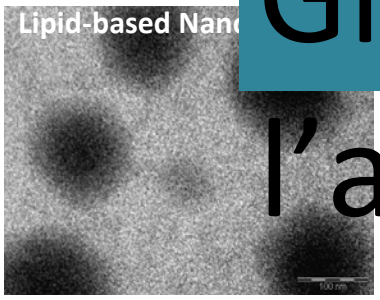
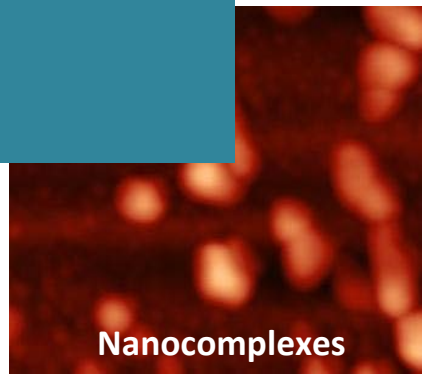


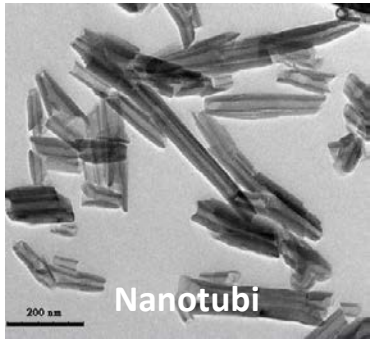


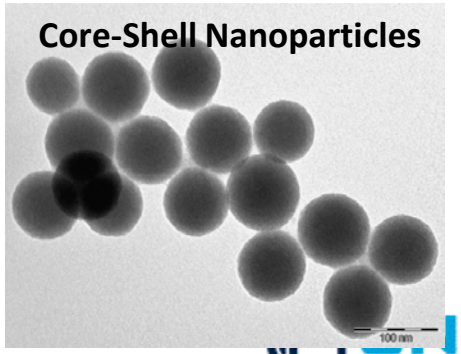


Grazie per l'attenzione









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