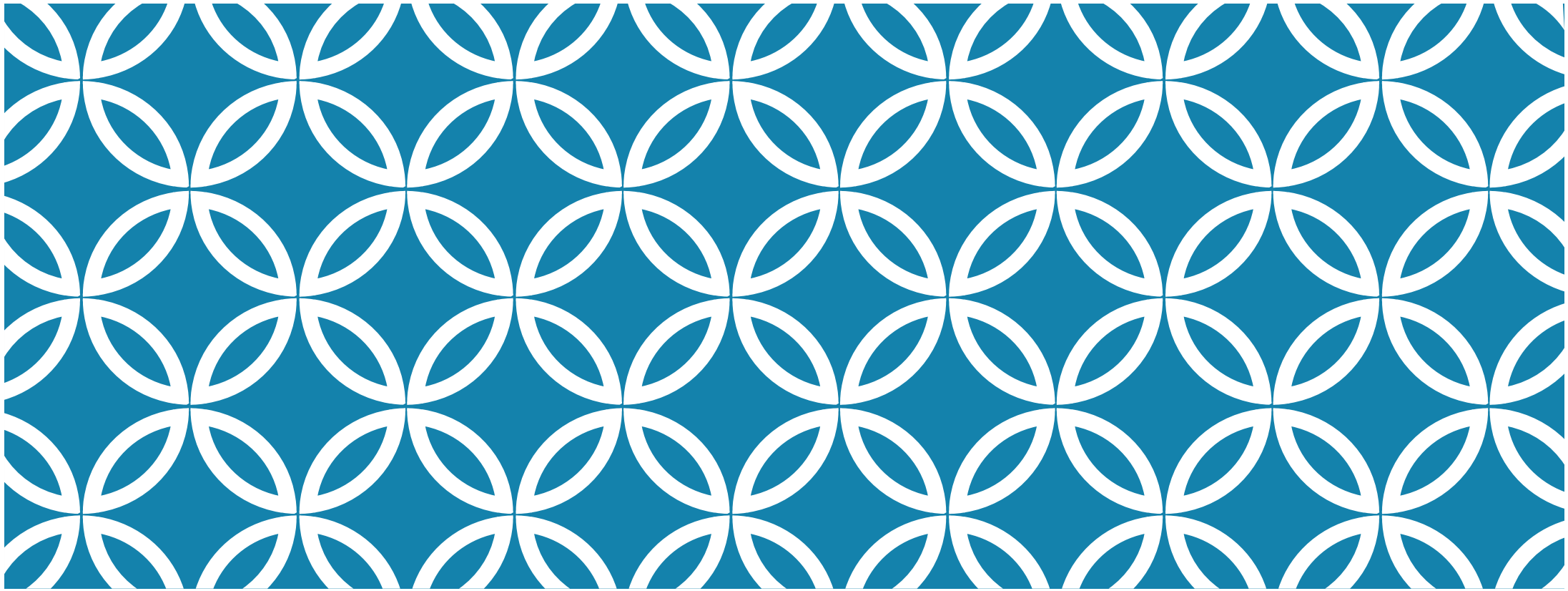


NANO

Maurizio Migliaccio, FIEEE

OUTLINE

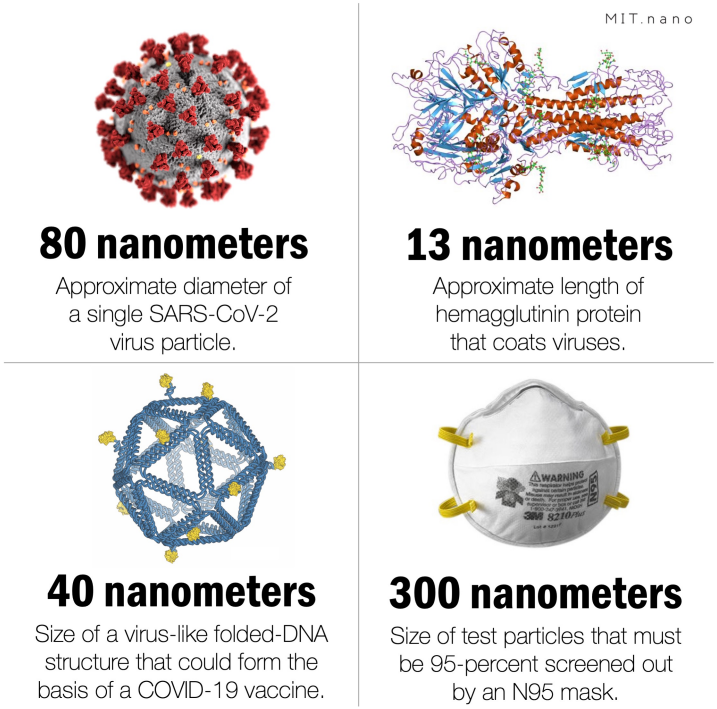
NANOTECHNOLOGY

Nanotechnology is the study and manipulation of individual atoms and molecules.

Nanotechnology involves the understanding and control of matter at the nanometer-scale.

The so-called nanoscale deals with dimensions between approximately 1 and 100 nanometers.

A nanometer is an extremely small unit of length - a billionth (10^{-9}) of a meter.



NANOTECHNOLOGY

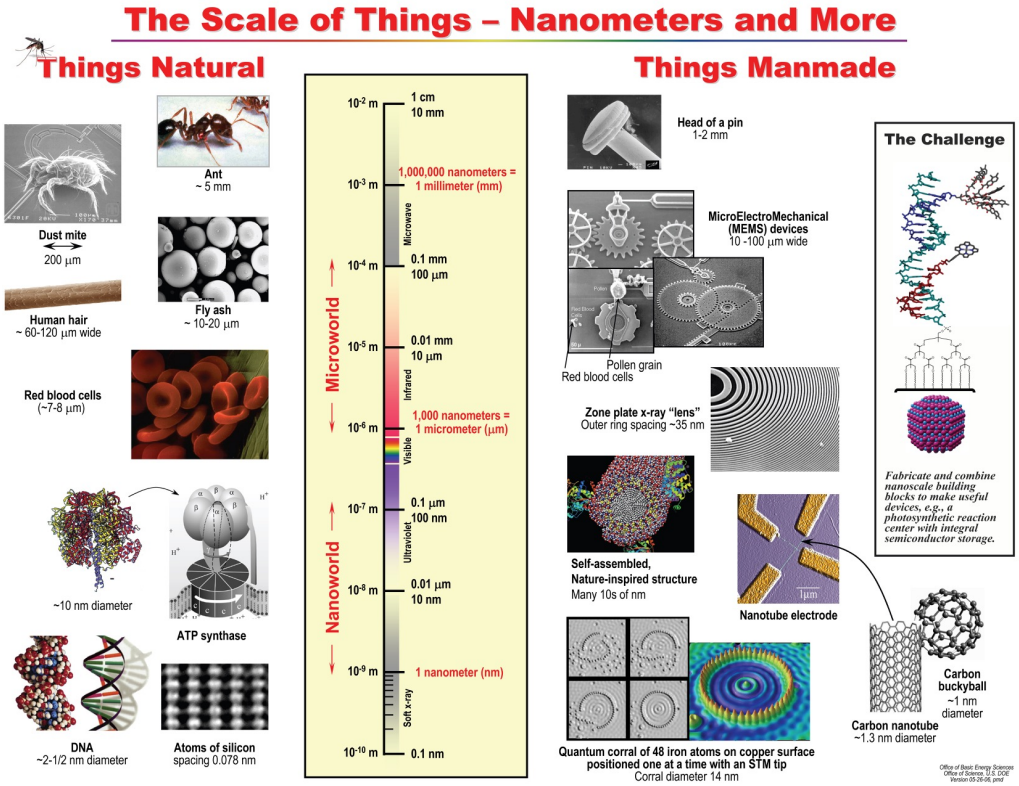
Scientists and engineers working at the nanoscale use their knowledge to design and build just like nature does: atom by atom and molecule by molecule.

On the nanometer-scale, materials may exhibit unusual properties.

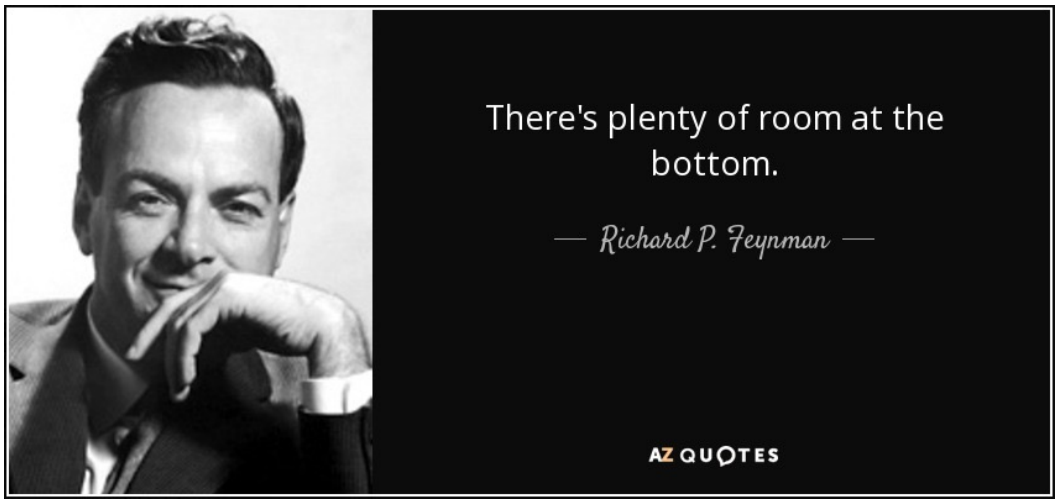
Nanotechnology is not microscopy.

"Nanotechnology is not simply working at ever smaller dimensions"

"Rather, working at the nanoscale enables scientists to utilize the unique physical, chemical, mechanical, and optical properties of materials that naturally occur at that scale."



HISTORY



U.S. physicist Richard Feynman is considered the father of nanotechnology.

He introduced the ideas and concepts behind nanotech in a 1959 talk titled "There's Plenty of Room at the Bottom."

Feynman did not use the term "nanotechnology," but described a process in which scientists would be able to manipulate and control individual atoms and molecules.

HISTORY

In the antiquities, nanoparticles were used by the Damascans to create swords with exceptionally sharp edges and the Romans to craft iridescent glassware.

Were these archaic artisans also nanotechnologists?

And what can today's scientists learn from such historic artefacts?

The stunning Lycurgus cup reveals a brilliant red when light passes through its sections of glass containing gold-silver alloyed nanoparticles.

Photograph: British Museum Images

HISTORY

The ancient empires of the world are remembered for their impressive large-scale feats of engineering: Macchu Picchu in Peru; the pyramids in Egypt; and the Parthenon in Greece to name a few. But the craftsmen of those eras were also skilled at engineering at the opposite end of the spectrum at the nanoscale.

The manipulation of material at the atomic and molecular scale to create new functions and properties sounds like it should be a profoundly modern concept. But artisans from the past also controlled matter at the tiniest scales.

By modern-day standards, they were working in a branch of nanotechnology called nanocomposites. These are bulk materials in which nanoscale particles are mixed to improve the properties of the overall or composite material.

HISTORY

There are a number of relatively famous examples of ancient artefacts which were created using nanocomposites: The Lycurgus cup, for example, is a stunning decorative Roman treasure from about AD400; it is made of a glass that changes colour when light is shone through it. The glass contains gold-silver alloyed nanoparticles, which are distributed in such a way to make the glass look green in reflected light but, when light passes through the cup, it reveals a brilliant red.

A corrosion resistant azure pigment known as Maya Blue, first produced in AD800, was discovered in the pre-columbian Mayan city of Chichen Itza. It is complex material containing clay with nanopores into which indigo dye was combined chemically to create an environmentally-stable pigment.

HISTORY

Maya blue (Spanish: azul maya) is a unique bright azure blue pigment manufactured by cultures of pre-Columbian Mesoamerica, such as the Mayans and Aztecs.

Despite time and the harsh weathering conditions, paintings coloured by Maya blue have not faded over time.

A warrior with Maya blue on the background

HISTORY

Of course, such craftsmen were highly skilled but they were not nanotechnologists. They did not know that they were working on the nanoscale. They developed materials by trial and error similar to evolution in biology. They didn't know the processes going on inside the solids.

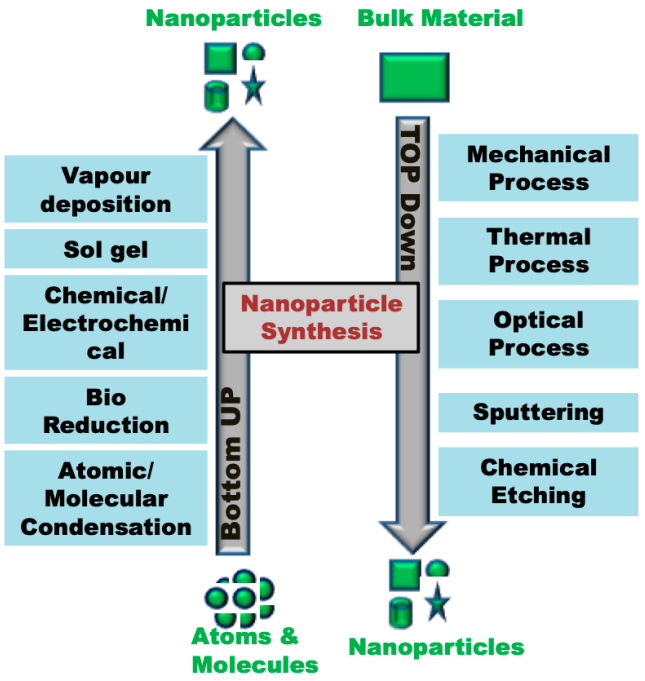
High-resolution microscopic analysis is used to reveal the nanostructure of these artefacts, but such analysis cannot tell us how they were made. "How did they dissolve these metals into the glass?" says Freestone of the Roman glassmakers who made the Lycurgus cup. "And how did they get such a homogenous distribution of nanoparticles? We can speculate but we really don't know for sure."

A disadvantage of using high-resolution microscopy is that samples must be milled down to a fraction of their original thickness, destroying part of the artefact. When the material is abundant, such as for weather-resistant Maya Blue, taking a little for analysis is not a big deal. But when these artefacts are rare, it's more difficult to justify.

MANIFACTURING

After Feynman had discovered this new field of research catching the interest of many scientists, two approaches have been developed describing the different possibilities for the synthesis of nanostructures.

These manufacturing approaches fall under two categories: *top-down* and *bottom-up*, which differ in degrees of quality, speed and cost.



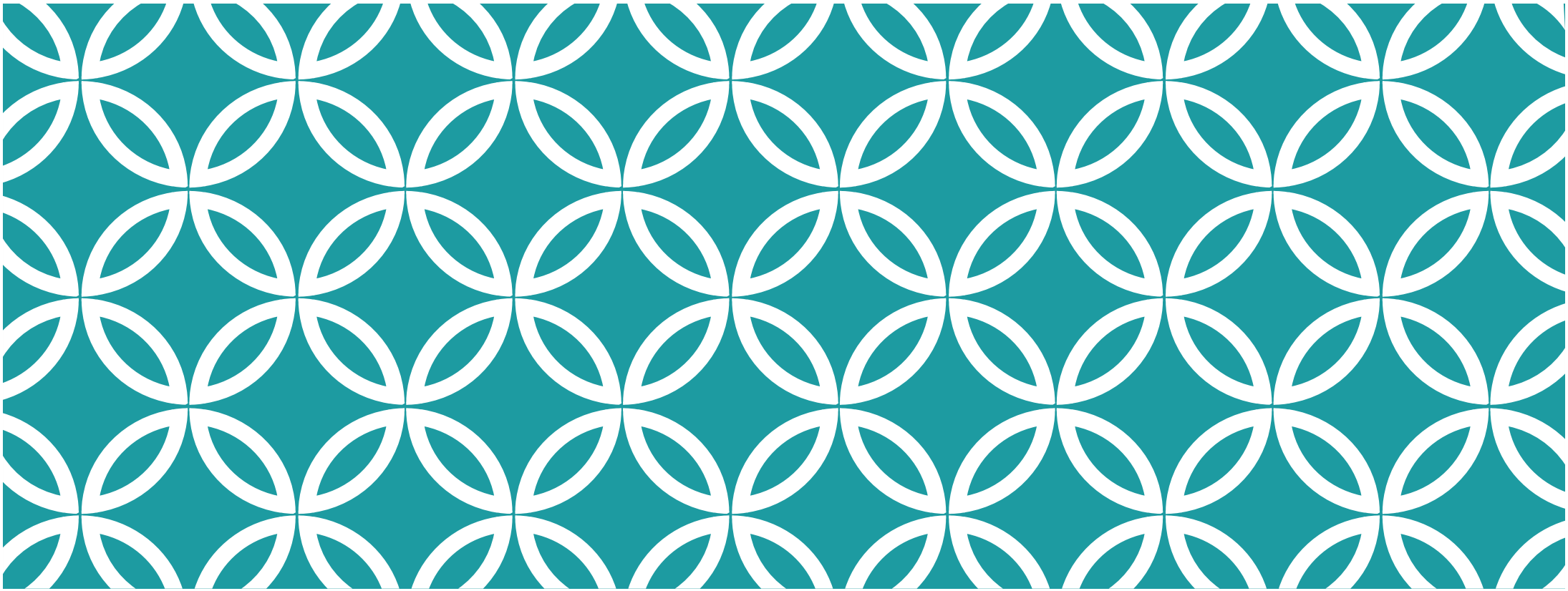
NANOMEDICINE

Recently, a number of studies highlighted the huge potential that nanotechnologies play in biomedicine for the diagnosis and therapy of many human diseases.

In this regard, bio-nanotechnology is considered by many experts as one of the most intriguing field of application of nanoscience.

During recent decades, the applications of nanotechnology in many biology related areas such as diagnosis, drug delivery, and molecular imaging are being intensively researched and offered excellent results.

Remarkable progresses have been made also in the field of nano-oncology by improving the efficacy of traditional chemotherapy drugs for a plethora of aggressive human cancers.



WHAT IS LIFE ?

WHAT IS LIFE?

That was the question posed by Erwin Schrödinger in a famous series of lectures delivered in Dublin, Ireland, in 1943, and published the following year as an influential book titled What Is Life?

Asked whether physics can explain life, most physicists would answer yes. The more pertinent question, however, is whether known physics is up to the job, or whether something fundamentally new is required.

In the 1930s many of the architects of quantum mechanics - most notably Niels Bohr, Eugene Wigner, and Werner Heisenberg - had a hunch that there is indeed something new and different in the physics of living matter.

Those questions go beyond mere academic interest.

WHAT IS LIFE?

The gulf between physics and biology is more than a matter of complexity; a fundamental difference in conceptual framework exists.

Physicists study life using concepts such as energy, entropy, molecular forces, and reaction rates.

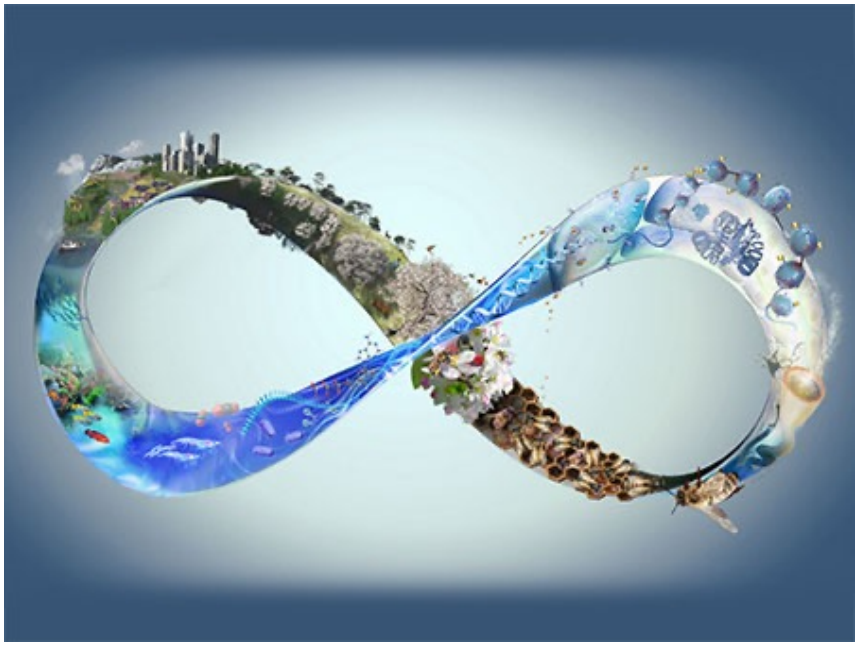
Biologists offer a very different narrative, with terms such as signals, codes, transcription, and translation - the language of information.

WHAT IS LIFE?

Life is invested in information storage and processing at all levels, not just in DNA.

Genes - DNA sequences that serve as encrypted instruction sets - can switch other genes on or off using chemical messengers, and they often form complex networks.

Those chemical circuits resemble electronic or computing components, sometimes constituting modules or gates that enact logical operations.



WHAT IS LIFE?

At the cellular level, a variety of physical mechanisms permit signaling and can lead to cooperative behavior.

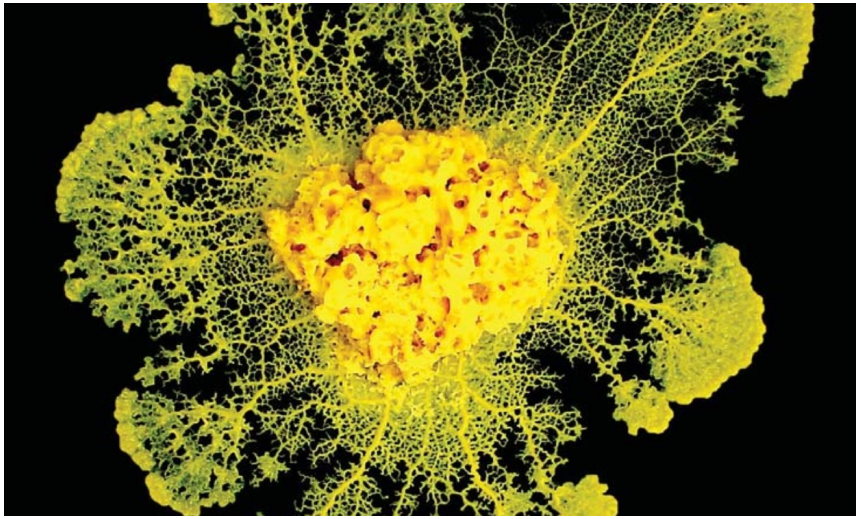
Slime molds, like the one shown in figure, provide a striking example. They are aggregations of single cells that can self-organize into striking shapes and sometimes behave coherently as if they were a single organism.

Likewise, social insects such as ants and bees exchange complex information and engage in collective decision making.

And human brains are information processing systems of staggering complexity.

The informational basis of life has led some scientists to pronounce the informal dictum, Life = Matter + Information.

Slime mold



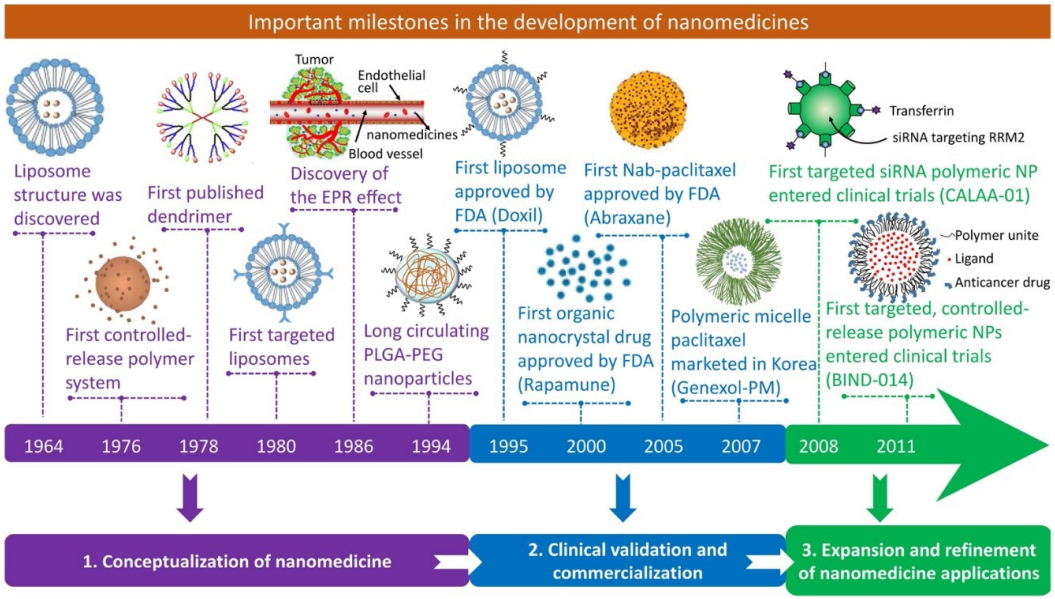
WHAT IS LIFE?

Since the time of Isaac Newton, a fundamental dualism has pervaded physics. Although physical states evolve with time, the underlying laws of physics are normally regarded as immutable. That assumption underlies Hamiltonian dynamics, trajectory integrability, and ergodicity.

But immutable laws are a poor fit for biological systems, in which dynamical patterns of information couple to time-dependent chemical networks and where expressed information—for example, the switching on of genes—can depend on global or systemic physical forces as well as local chemical signaling.

Biological evolution, with its open-ended variety, novelty, and lack of predictability, also stands in stark contrast to the way that nonliving systems change over time. Yet biology is not chaos: many examples of rules at work can be found.

NANOMEDICINE



Nanobiotechnology, bionanotechnology, and nanobiology are terms that refer to the intersection of nanotechnology and biology.

This discipline helps to indicate the merger of biological research with various fields of nanotechnology.

Concepts that are enhanced through nanobiology include: nanodevices (such as biological machines), nanoparticles, and nanoscale phenomena that occurs within the discipline of nanotechnology.

This technical approach to biology allows scientists to imagine and create systems that can be used for biological research.

Biologically inspired nanotechnology uses biological systems as the inspirations for technologies not yet created.

NANOMEDICINE

Engineered nanomaterials hold significant promise to improve disease diagnosis and treatment specificity.

Nanotechnology could help overcome the limitations of conventional delivery - from large-scale issues such as biodistribution to smaller-scale barriers such as intracellular trafficking - through cell-specific targeting, molecular transport to specific organelles and other approaches.

These initiatives have supported the recent efforts to investigate and improve nanotechnology, of which nanoparticles (NPs) constitute a significant portion of reported research and advancement.

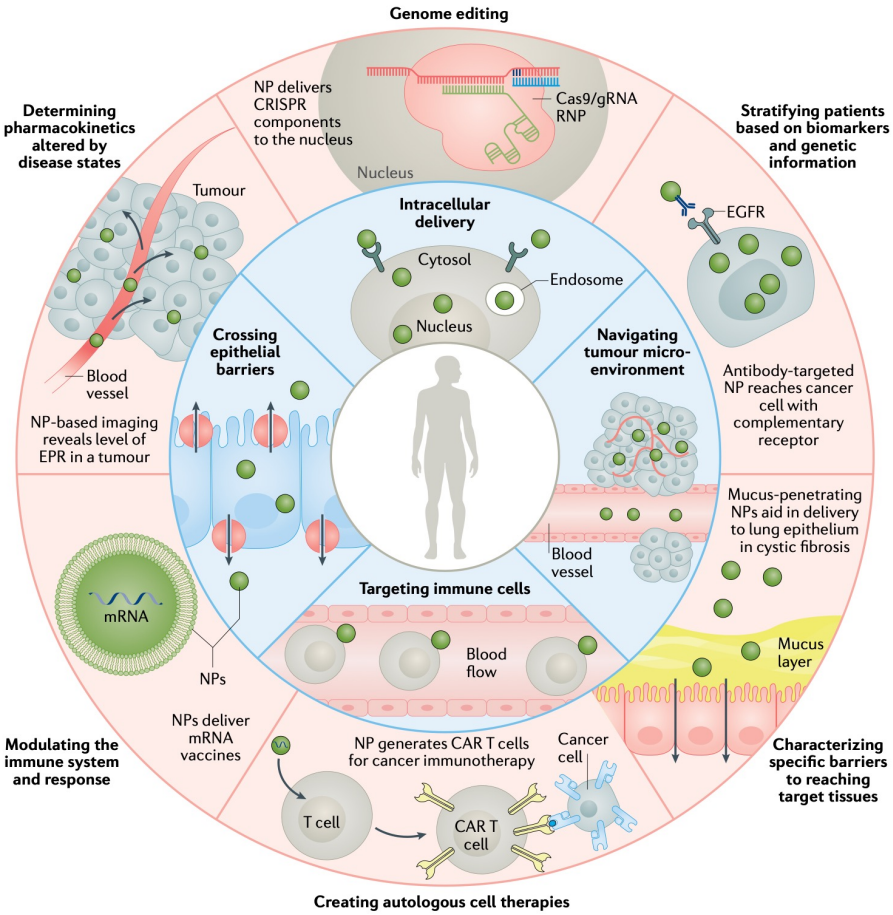
The goal of precision medicine is to utilize patient information — such as genetic profile, environmental exposures or comorbidities — to develop an individualized treatment plan.

NANOMEDICINE

Biological barriers to precision medicine applications.

Overview highlighting some of the biological barriers that nanoparticles (NPs) can overcome (inner ring) and precision medicine applications that may benefit from NPs (outer ring). Intelligent NP designs that improve delivery have the potential to enhance the performance of precision medicines and, thus, accelerate their clinical translation.

CAR, chimeric antigen receptor; EGFR, epidermal growth factor receptor; EPR, enhanced permeation and retention; gRNA, guide RNA; RNP, ribonucleoprotein.

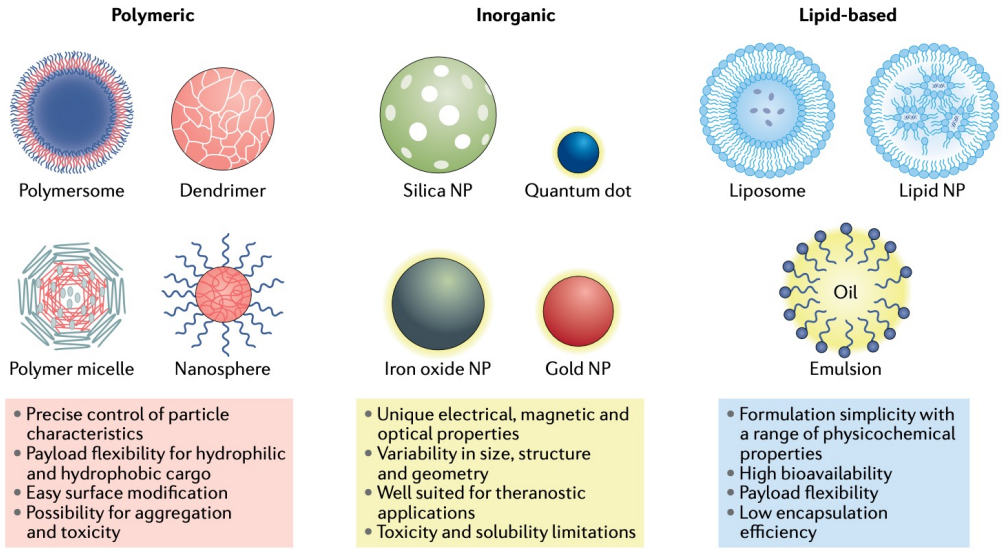


NANOMEDICINE

Classes of NPs

Each class of nanoparticle (NP) features multiple subclasses, with some of the most common highlighted here.

Each class has numerous broad advantages and disadvantages regarding cargo, delivery and patient response.



LIPID-BASED NPS

Lipid-based NPs include various subset structures but are most typically spherical platforms comprising at least one lipid bilayer surrounding at least one internal aqueous compartment.

As a delivery system, lipid-based NPs offer many advantages including formulation simplicity, self-assembly, *biocompatibility*, high bioavailability, ability to carry large payloads and a range of physicochemical properties that can be controlled to modulate their biological characteristics. For these reasons, *lipid-based NPs are the most common class of FDA-approved nanomedicines*.

POLYMERIC NPS

Polymeric NPs can be synthesized from natural or synthetic materials, as well as monomers or preformed polymers — allowing for a wide variety of possible structures and characteristics.

They can be formulated to enable precise control of multiple NP features and are generally good delivery vehicles because they are biocompatible and have simple formulation parameters.

Polymeric NPs also have variable drug delivery capabilities.

The most common forms of polymeric NPs are nanocapsules (cavities surrounded by a polymeric membrane or shell) and nanospheres (solid matrix systems).

Overall, polymeric NPs are ideal candidates for drug delivery because they are biodegradable, water soluble, biocompatible, biomimetic and stable during storage. Their surfaces can be easily modified for additional targeting — allowing them to deliver drugs, proteins and genetic material to targeted tissues, which makes them useful in cancer medicine, gene therapy and diagnostics. However, disadvantages of polymeric NPs include an increased risk of particle aggregation and toxicity. *Only a small number of polymeric nano-medicines are currently FDA approved and used in the clinic*.

INORGANIC NPS

Inorganic materials such as gold, iron and silica have been used to synthesize nanostructured materials for various drug delivery and imaging applications.

These inorganic NPs are precisely formulated and can be engineered to have a wide variety of sizes, structures and geometries.

Due to their magnetic, radioactive or plasmonic properties, inorganic NPs are uniquely qualified for applications such as diagnostics, imaging and photo-thermal therapies.

They are limited in their clinical application by low solubility and toxicity concerns, especially in formulations using heavy metals.

NANOMEDICINES

FDA-approved nanomedicines.

Drug	Company	Application	Date of first approval
Lipid-based			
Doxil	Janssen	Kaposi's sarcoma, ovarian cancer, multiple myeloma	1995
DaunoXome	Galen	Kaposi's sarcoma	1996
AmBisome	Gilead Sciences	Fungal/protozoal infections	1997
Visudyne	Bausch and Lomb	Wet age-related macular degeneration, myopia, ocular histoplasmosis	2000
Marqibo	Acrotech Biopharma	Acute lymphoblastic leukaemia	2012
Onivyde	Ipsen	Metastatic pancreatic cancer	2015
Vyxeos	Jazz Pharmaceuticals	Acute myeloid leukaemia	2017
Onpattro	Alnylam Pharmaceuticals	Transthyretin-mediated amyloidosis	2018
Polymer-based			
Oncaspar	Servier Pharmaceuticals	Acute lymphoblastic leukaemia	1994
Copaxone	Teva	Multiple sclerosis	1996
PegIntron	Merck	Hepatitis C infection	2001
Eligard	Tolmar	Prostate cancer	2002
Neulasta	Amgen	Neutropenia, chemotherapy induced	2002
Abraxane	Celgene	Lung cancer, metastatic breast cancer, metastatic pancreatic cancer	2005
Cimiza	UCB	Crohn's disease, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis	2008
Plegridy	Biogen	Multiple sclerosis	2014
ADYNOVATE	Takeda	Haemophilia	2015
Inorganic			
INFeD	Allergan	Iron-deficient anaemia	1992
DexFerrum	American Regent	Iron-deficient anaemia	1996
Ferrlecit	Sanofi	Iron deficiency in chronic kidney disease	1999
Venofer	American Regent	Iron deficiency in chronic kidney disease	2000
Feraheme	AMAG	Iron deficiency in chronic kidney disease	2009
Injectafer	American Regent	Iron-deficient anaemia	2013

NPS

Being much smaller than the wavelengths of visible light (400-700 nm), nanoparticles cannot be seen with ordinary optical microscopes, requiring the use of electron microscopes or microscopes with laser.

The properties of nanoparticles often differ markedly from those of larger particles of the same substance. Since the typical diameter of an atom is between 0.15 and 0.6 nm, a large fraction of the nanoparticle's material lies within a few atomic diameters of its surface. Therefore, the properties of that surface layer may dominate over those of the bulk material. This effect is particularly strong for nanoparticles dispersed in a medium of different composition since the interactions between the two materials at their interface also becomes significant.

Nanoparticles occur widely in nature and are objects of study in many fields.

NPS

Non-spherical nanoparticles (e.g., prisms, cubes, rods etc.) exhibit shape-dependent and size-dependent (both chemical and physical) properties (anisotropy).

Anisotropic nanoparticles display a specific absorption behavior and stochastic particle orientation under unpolarized light.

SCATTERING

Mie scattering, also known as Lorenz-Mie scattering, is a complete and mathematically rigorous solution to the problem of scattering an electromagnetic wave on a sphere or cylinder.

The theory that describes this type of scattering takes its name from the German physicist Gustav Mie who was the first to publish the complete solution in 1908.

Danish physicist Ludvig Lorenz and others independently developed the theory of electromagnetic plane wave scattering by a dielectric sphere.

https://en.wikipedia.org/wiki/Codes_for_electromagnetic_scattering_by_spheres

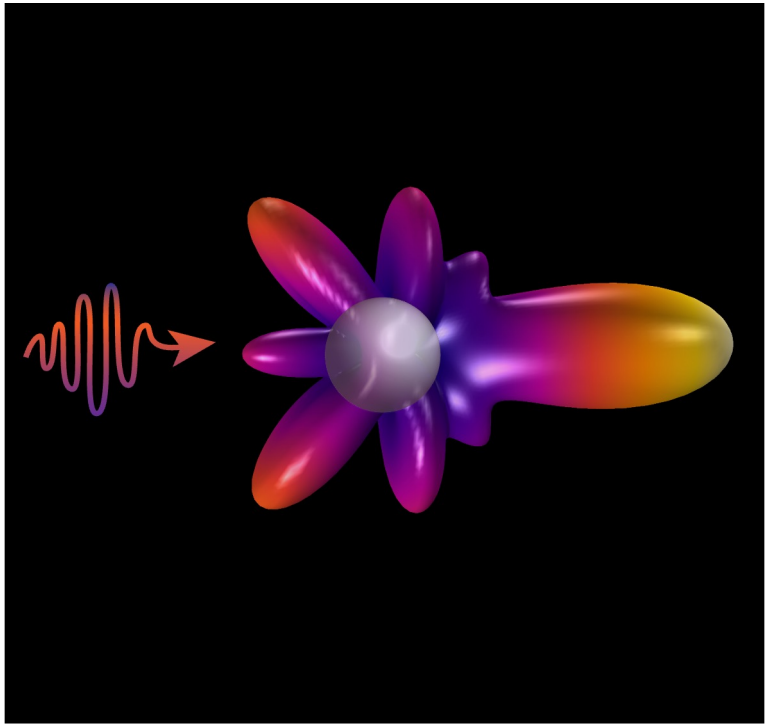
Gustav Adolf Feodor Wilhelm Ludwig Mie (29 September 1868 – 13 February 1957) was a German physicist.

SCATTERING

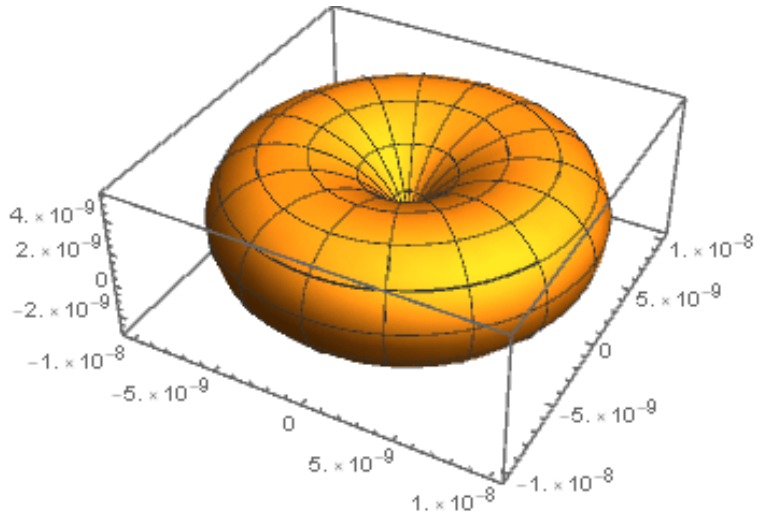
Mie scattering, artistic view (under linearly polarized incident plane wave).

The notable features of these results are the Mie resonances, sizes that scatter particularly strongly or weakly.

This is in contrast to Rayleigh scattering for small particles and Rayleigh–Gans–Debye scattering for large particles.



SCATTERING



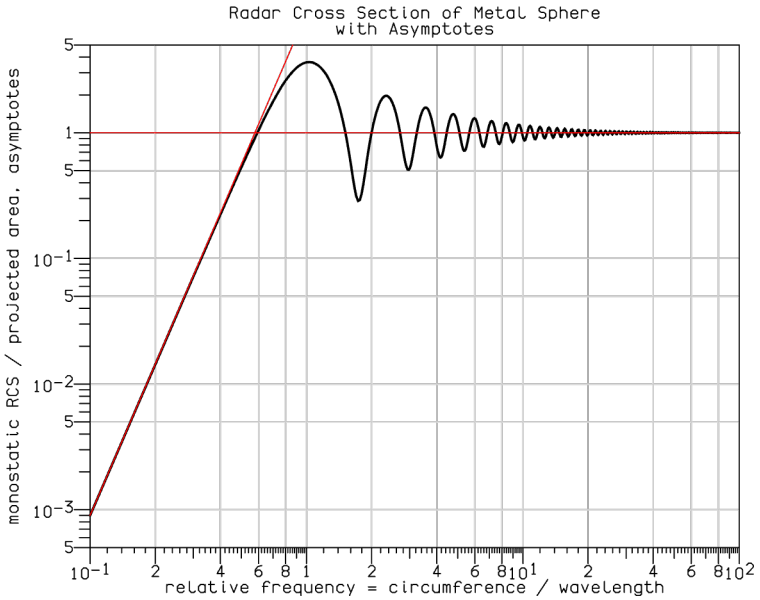
Mie scattering as a function of particle's radius. Along one cycle, the particle diameter changes from 0.1 wavelength to 1 wavelength. The sphere's refractive index is 1.5

SCATTERING

Mie scattering is valid for diffuser centers of any size and, in the limit in which these are much smaller than the incident wavelength, Rayleigh scattering is obtained (which is valid only for point diffusers).

In the low-frequency Rayleigh scattering limit, where the circumference is less than the wavelength, the normalized RCS is $\sigma/(\pi R^2) \sim 9(kR)^4$. In the high-frequency optical limit $\sigma/(\pi R^2) \sim 1$.

Monostatic radar cross section (RCS) of a perfectly conducting metal sphere as a function of frequency (calculated by Mie theory).



SCATTERING

Rayleigh scattering describes the elastic scattering of light by spheres that are much smaller than the wavelength of light. The intensity I of the scattered radiation is given by

$$I = I_o \left(\frac{1 + cos^2\theta}{2R^2} \right) \left(\frac{2\pi}{\lambda} \right)^4 \left(\frac{n^2 - 1}{n^2 + 2} \right)^2 \left(\frac{d}{2} \right)^6$$

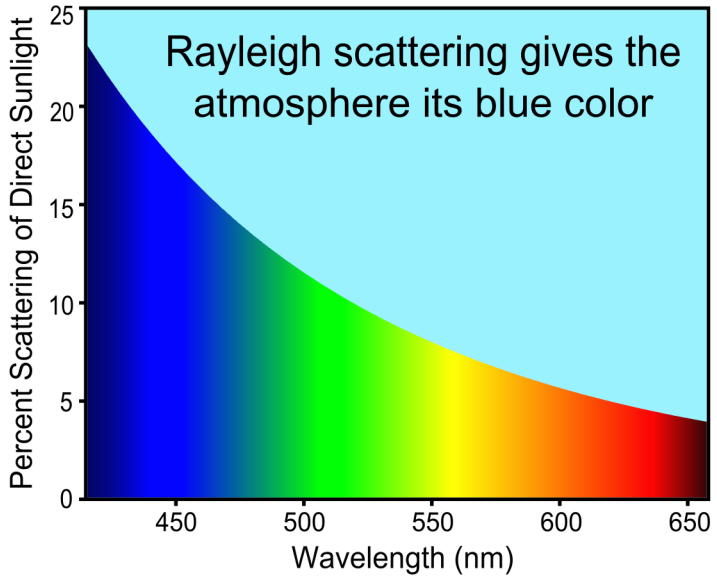
where I_0 is the light intensity before the interaction with the particle, R is the distance between the particle and the observer, θ is the scattering angle, λ is the wavelength of light under consideration, n is the refractive index of the particle, and d is the diameter of the particle.

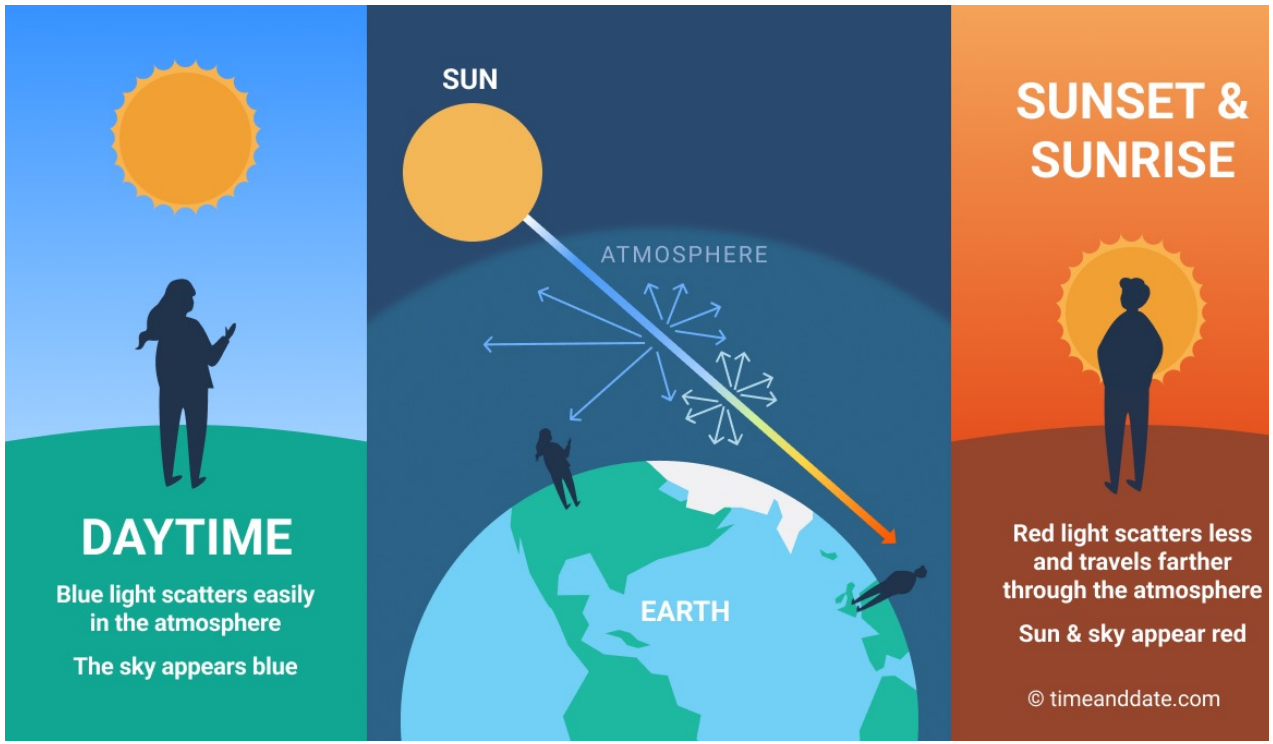
SCATTERING

The Rayleigh scattering model breaks down when the particle size becomes larger than around 10% of the wavelength of the incident radiation.

The strong wavelength dependence of the scattering ($\sim\lambda^{-4}$) means that shorter (blue) wavelengths are scattered more strongly than longer (red) wavelengths. This results in the indirect blue light coming from all regions of the sky.

The proportion of blue light scattered by the atmosphere relative to red light.





SCATTERING

Rayleigh scattering is inversely proportional to the fourth power of wavelength, so that shorter wavelength violet and blue light will scatter more than the longer wavelengths (yellow and especially red light).

However, the Sun, like any star, has its own spectrum and so I_0 in the scattering formula above is not constant but falls away in the violet.

The reddening of the sun is intensified when it is near the horizon because the light being received directly from it must pass through more of the atmosphere. The effect is further increased because the sunlight must pass through a greater proportion of the atmosphere nearer the earth's surface, where it is denser. This removes a significant proportion of the shorter wavelength (blue) and medium wavelength (green) light from the direct path to the observer. The remaining unscattered light is therefore mostly of longer wavelengths and appears more red.

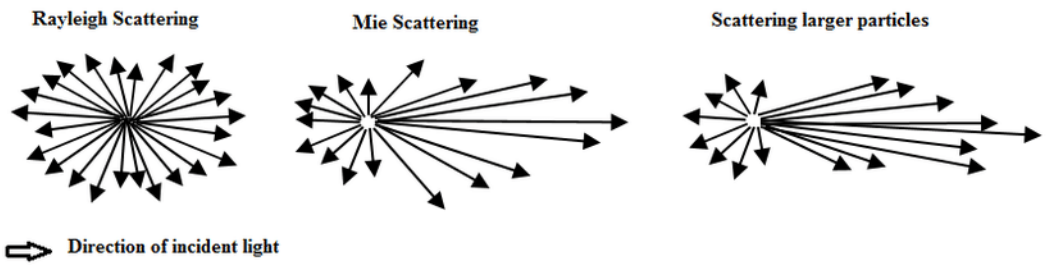
SCATTERING

In the case of particles with dimensions greater than this, Mie's scattering model can be used to find the intensity of the scattered radiation.

The intensity of Mie scattered radiation is given by the summation of an infinite series of terms rather than by a simple mathematical expression.

It can be shown, however, that scattering in this range of particle sizes differs from Rayleigh scattering in several respects: it is roughly independent of wavelength and it is larger in the forward direction than in the reverse direction.

The greater the particle size, the more of the light is scattered in the forward direction.

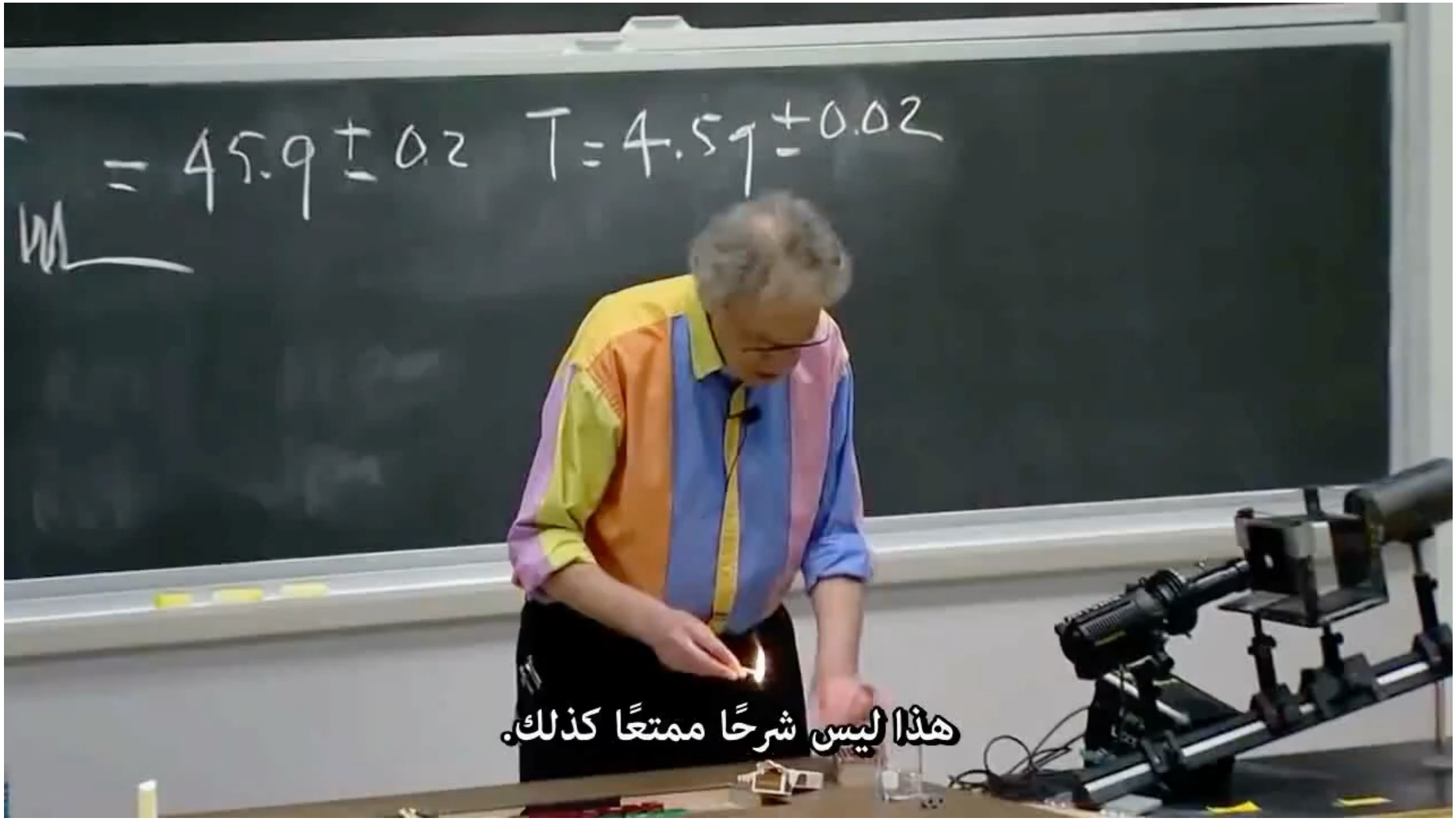


SCATTERING

It can be seen from the above equation that Rayleigh scattering is strongly dependent upon the size of the particle and the wavelengths.

The intensity of the Rayleigh scattered radiation increases rapidly as the ratio of particle size to wavelength increases.

Furthermore, the intensity of Rayleigh scattered radiation is identical in the forward and reverse directions.


= 45.9 ± 0.2
T = 4.59 ± 0.02
هذا ليس شرحًا ممتعًا كذلك.

NANOMEDICINE

Even under normal physiological conditions, effective biodistribution and drug delivery are difficult to achieve as NPs face both physical and biological barriers — including shear forces, protein adsorption and rapid clearance — that limit the fraction of administered NPs that reach the target therapeutic site.

These barriers are often altered in disease states and can be even more difficult to overcome with a generalized, one-size-fits-all approach.

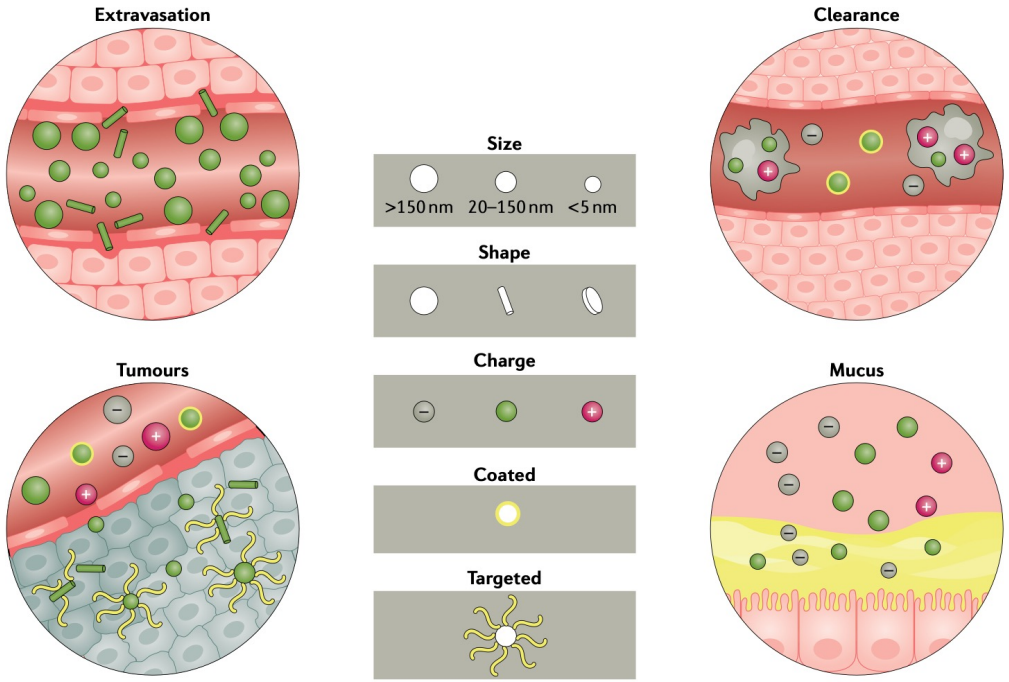
NANOMEDICINE

Furthermore, these changes in biological barriers vary not just across diseases but also on a patient-to-patient basis, and they can occur at the systemic, microenvironmental and cellular levels, making them hard to isolate and characterize broadly. Understanding the biological barriers faced both generally and on a patient-specific level allows for the design of optimally engineered NP platforms.

NANOMEDICINE

NP characteristics impact distribution.

Factors such as size, shape, charge and surface coating determine what happens to nanoparticles (NPs) in the circulation, including clearance, and how the NPs interact with local barriers such as the tumour microenvironment or mucus layers. A few general trends are highlighted here: spherical and larger NPs marginate more easily during circulation, whereas rod-shaped NPs extravasate more readily (top left); and uncoated or positively charged NPs are cleared more quickly by macrophages (top right). In terms of local distribution, in general, rod-shaped, neutral and targeted NPs penetrate tumours more readily (bottom left) whereas positively charged, smaller and coated NPs more easily traverse mucosal barriers (bottom right).



NANOMEDICINE

Cancer remains the second leading cause of death worldwide.

Cancer is heterogeneous, and the development of effective cancer therapies is very challenging partially because of this complexity.

However, precision medicine has emerged as a promising approach, and targeted chemotherapeutics have been developed that can treat patients who express specific biomarkers.

The first drug of this type, imatinib (Gleevec; Novartis), is given to patients with chronic myeloid leukaemia who express the BCR–ABL fusion protein from the Philadelphia chromosome.

FDA approval of imatinib opened the field for many other successful targeted chemotherapeutics.

However, these therapies and others could be more effective if delivery is improved.

NANOMEDICINE

Complex drug delivery mechanisms are being developed, including the ability to get drugs through cell membranes and into cell cytoplasm.

Drug delivery systems may also be able to prevent tissue damage through regulated drug release; reduce drug clearance rates; or lower the volume of distribution and reduce the effect on non-target tissue.

However, the biodistribution of these nanoparticles is still imperfect due to the complex host's reactions to nano- and microsized materials and the difficulty in targeting specific organs in the body.

NANOMEDICINE

Nanoparticles are made to be long-lasting, but this causes them to be trapped within organs, specifically the liver and spleen, as they cannot be broken down or excreted.

Magnetic targeted delivery of magnetic nanoparticles to the tumor site under the influence of inhomogeneous stationary magnetic fields may lead to enhanced tumor growth.

In order to circumvent the pro-tumorigenic effects, alternating electromagnetic fields should be used.

NANOMEDICINE

NANOMEDICINE

Nanotechnology research and development have increased over the last three decades.

Nanoparticles (NPs) have been developed to overcome the problems of targeting and efficiency, with reduced toxicity.

In the last decade, their applicability has been focused on the biomedical and pharmaceutical fields, used as drug delivery systems, diagnostic tools, and implants.

Nanoparticles can be made of different materials.

The use of nanoparticle-based drug delivery systems has increased due to their controlled release of reservoir content, leading to a decrease in undesirable side effects.

NANOMEDICINE

Nanoparticle formulation requires full characterization of its size, surface charge, shape, and distribution.

Usually, only a small fraction of the nanoparticles injection dose (<0.7%) reaches the target.

This shows that NPs have some organism barriers to overcome, such as unspecific distribution, interstitial fluid pressure, cellular internalization, and drug efflux pumps, before achieving therapeutic effect.

Nanoparticles have size-related properties influencing their mode of action and *in vivo* lifetime.

NANOMEDICINE

The optimal size for drug delivery systems is considered to be broadly between 10 and 1000nm.

Low sizes allow NPs to cross cell membranes and avoid detection by the reticuloendothelial system (RES), increasing the drug circulation lifetime. However, they must not be too small, in order to avoid rapid distribution into lymph nodes, being eliminated by fast renal clearance.

On the other hand, nanoparticles larger than 100 nm are more prone to accumulate at the site of injection or trapped by the spleen, lung, and liver macrophages.

In conclusion, size must be optimized taking into account the amount of cargo to be delivered and the desirable biodistribution.

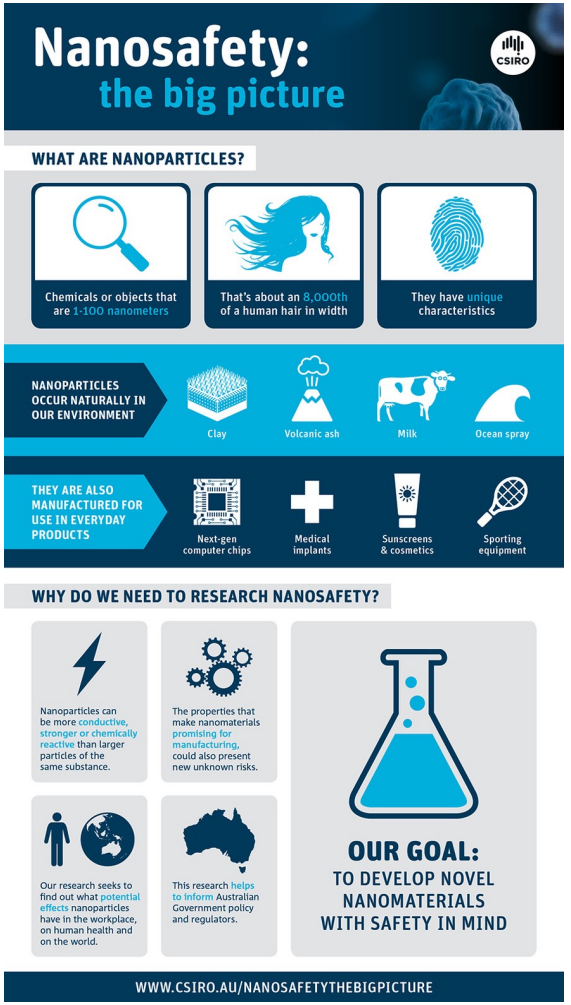
NANOMEDICINE

The unique physicochemical properties and nanoscale effects have drawn interest on nanoparticle as drug delivery systems for the treatment of diseases such as cancer, cardiovascular diseases, pathogenic infections, and diabetes.

Despite the raised interest in nanoparticle development, not so many have been approved for therapeutic use.

Light scattering approaches to characterize nanoparticle suspensions and their applicability on nanoparticle development against infectious and cardiovascular diseases is an important tool.

NANOSAFETY


Nanosafety:
the big picture
CSIRO
WHAT ARE NANOPARTICLES?
Chemicals or objects that are 1-100 nanometers
That's about an 8,000th of a human hair in width
They have unique characteristics
NANOPARTICLES OCCUR NATURALLY IN OUR ENVIRONMENT
Clay
Volcanic ash
Milk
Ocean spray
THEY ARE ALSO MANUFACTURED FOR USE IN EVERYDAY PRODUCTS
Next-gen computer chips
Medical implants
Sunscreens & cosmetics
Sporting equipment
WHY DO WE NEED TO RESEARCH NANOSAFETY?
Nanoparticles can be more conductive, stronger or chemically reactive than larger particles of the same substance.
The properties that make nanomaterials promising for manufacturing, could also present new unknown risks.
Our research seeks to find out what potential effects nanoparticles have in the workplace, on human health and on the world.
This research helps to inform Australian Government policy and regulators.
OUR GOAL:
TO DEVELOP NOVEL NANOMATERIALS WITH SAFETY IN MIND
WWW.CSIRO.AU/NANOSAFETYTHEBIGPICTURE

NANOSAFETY

While nanotechnology and the production of nanoparticles are growing exponentially, research into the toxicological impact and possible hazard of nanoparticles to human health and the environment is still in its infancy.

Proper characterisation of the nanomaterial, as well as understanding processes happening on the nanoparticle surface when in contact with living systems, is crucial to understand possible toxicological effects.

Dose as a key parameter is essential in hazard identification and risk assessment of nanotechnologies. Understanding nanoparticle pathways and entry routes into the body requires further research in order to inform policy makers and regulatory bodies about the nanotoxicological potential of certain nanomaterials.

NANOSAFETY

Toxicology traditionally addresses adverse poisoning effects of chemicals to humans, animals and the environment.

Historically, toxicology is often associated with Paracelsus and the concept of dose and dose response. He is attributed with having coined the phrase "the dose makes the poison", implying a linear relationship.

However toxicological dose responses can be complex and decidedly non-linear especially in the low and high dose range.

Paracelsus (c. 1493 – 24 September 1541), born Philippus Aureolus Theophrastus Bombastus von Hohenheim, was a Swiss physician, alchemist.

NANOSAFETY

While we largely understand the properties of bulk materials and/or chemicals at the molecular level, there are new properties of materials being discovered in the zone between “molecule” and “bulk”—that is the nanoscale.

Growing concerns about possible adverse health effects of nano-particles and nanostructures were derived from prior experience with, for example, asbestos and air pollution.

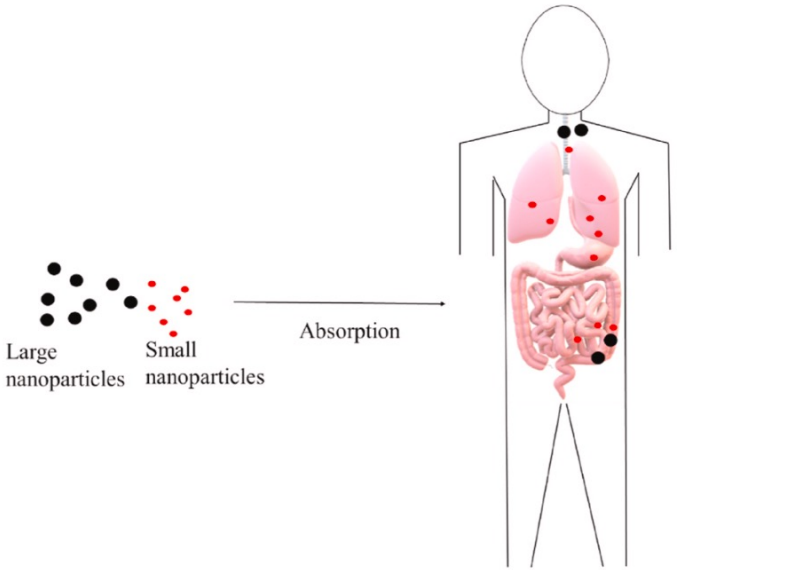
Apart from their atomic composition, nanomaterials have been categorized according to whether the nanostructure is immobilized within a bulk material, for example as part of a surface of a bulk material or, alternatively, comprised of free, unbound particles capable of mobility within the environment and the body, with diameters in the nanometre range.

It is the latter which are the most concerning, from a toxicological point of view.

NANOSAFETY

Interaction mechanisms between nanoparticles and living systems are not yet fully understood. The complexity comes with the particles' ability to bind and interact with biological matter and change their surface characteristics, depending on the environment they are in.

A critical step in nanotoxicology is to characterize the nanomaterial under examination and this is much more difficult than is the case in classical toxicology because of the multitude of variables in the parameter space. These include: particle size, roughness, shape, charge, composition and surface coating. The latter can change depending upon the matrix into which it is introduced.

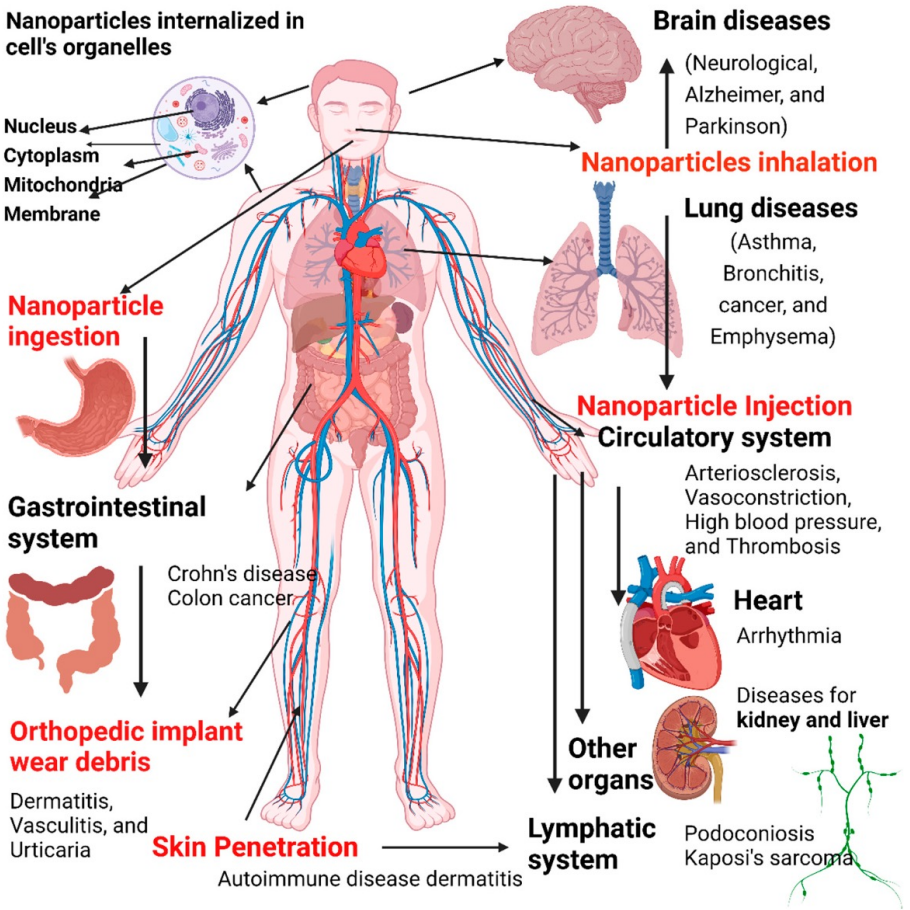


Absorption of small sized nanoparticles than large ones inside the organs

NANOSAFETY

Schematic representation of the nanoparticle exposure routes in the human body, the organs/tissues concerned, and the diseases linked to such exposure (based on the findings of epidemiological, in vivo, and in vitro studies).

Experimental findings suggest that fine-sized particles are more harmful.



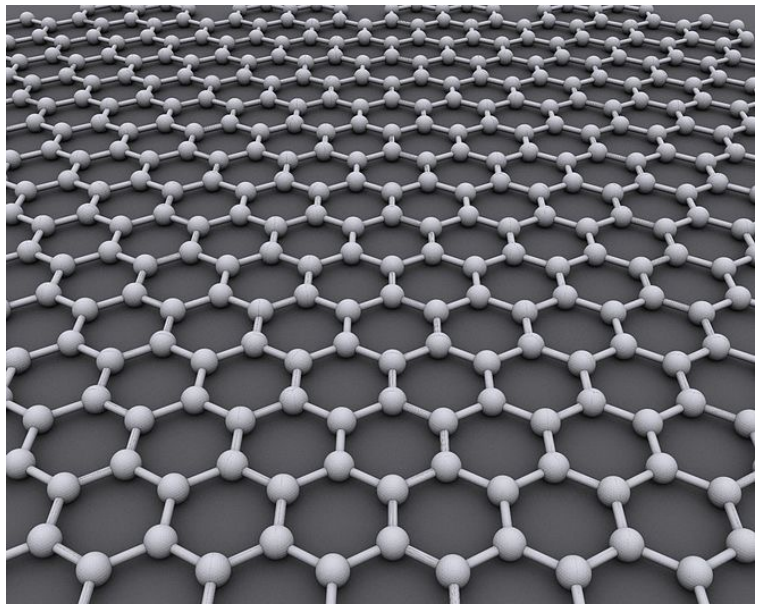
NANOSAFETY

The graphene-family nanomaterials (GFNs) are widely used in many fields, especially in biomedical applications.

Graphene, which is isolated from crystalline graphite, is a flat monolayer composed of single-atom-thick, two-dimensional sheets of a hexagonally arranged honeycomb lattice.

Graphene-based materials usually have sizes ranging from several to hundreds of nanometer and are 1-10 nm thick, which is also the definition of 'nanoparticles' or 'nanomaterials'.

Molecular model of graphene, with hexagonal cell structure



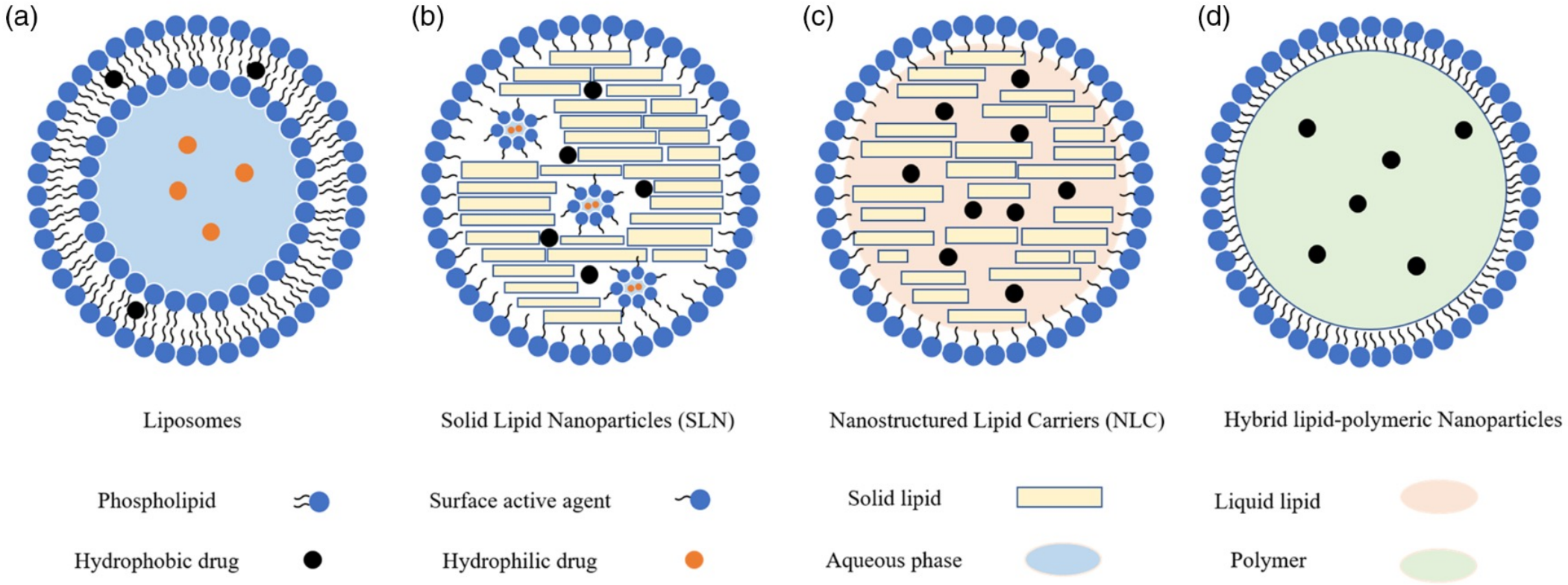
NANOSAFETY

Due to their exceptional physical and chemical properties, graphene materials have been widely used in various fields, including biomedical applications.

The toxicological mechanisms of GFNs demonstrated in recent studies mainly contain inflammatory response, DNA damage, apoptosis, autophagy and necrosis etc., and those mechanisms can be collected to further explore the complex signaling pathways network regulating the toxicity of GFNs.

Due to their nanosize, GFNs can reach deeper organs by passing through the normal physiological barriers, such as the blood-air barrier, blood-testis barrier, blood-brain barrier and blood-placental barrier.

Although some physicochemical properties and the toxicity of GFNs have been well studied by many scholars, the exact mechanisms underlying the toxicity of GFNs remain obscure.



NANOSAFETY

Lipid nanoparticles as drug delivery systems offer many attractive benefits such as great biocompatibility, ease of preparation, feasibility of scale-up, nontoxicity, and targeted delivery.

NANOSAFETY

Lipid-based nanoparticles such as liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) have demonstrated tremendous clinical success in delivering both hydrophobic and hydrophilic therapeutics.

The first FDA-approved nanodrug, Doxil, is a doxorubicin (DOX)-loaded PEGylated liposome for treating breast cancer, ovarian cancer, and other solid tumors.

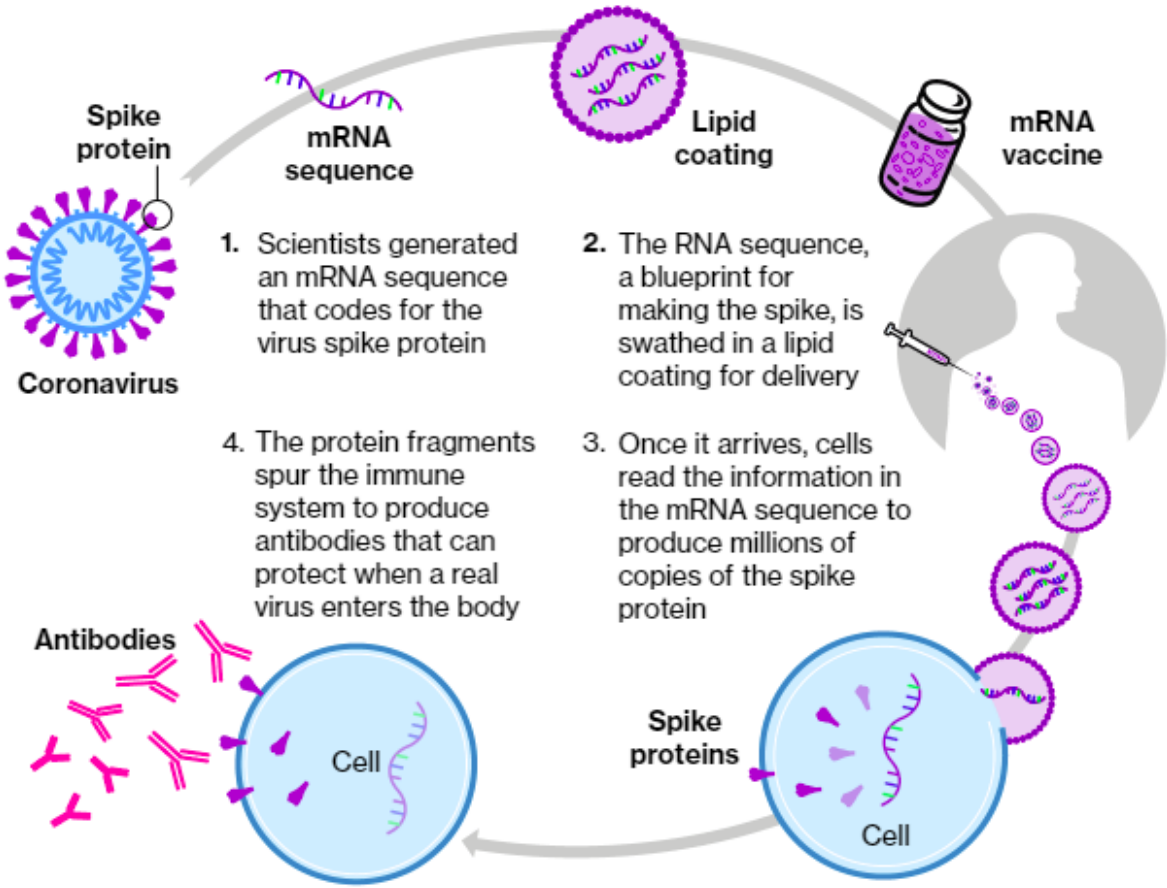
Compared to free DOX, the PEGylated liposomal doxorubicin Doxil offers several benefits including dramatic reduction of cardiotoxicity, prolonged retention time in human plasma, and passively targeted delivery to tumors by taking advantage of the enhanced permeability and retention (EPR) effect.

The clinical approval of Doxil in 1995 represents a big milestone for cancer nanomedicine and lipid-based drug delivery systems.

NANOSAFETY

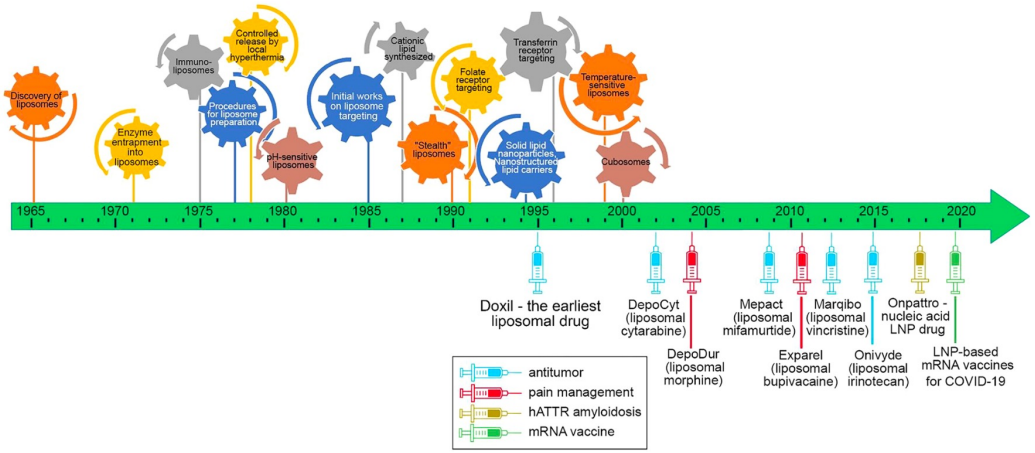
On the other hand, lipid nanoparticles (LNPs) have also been recognized as an ideal carrier for nucleic acids like DNA, mRNA, and siRNA due to their outstanding biocompatibility, biodegradability, and entrapment efficiency.

More recently mRNA COVID-19 vaccines developed by BioNTech/Pfizer and Moderna have been issued emergency use authorizations, and both of them use LNPs as mRNA carriers.[



Sources: Pfizer, Bloomberg research

NANOSAFETY

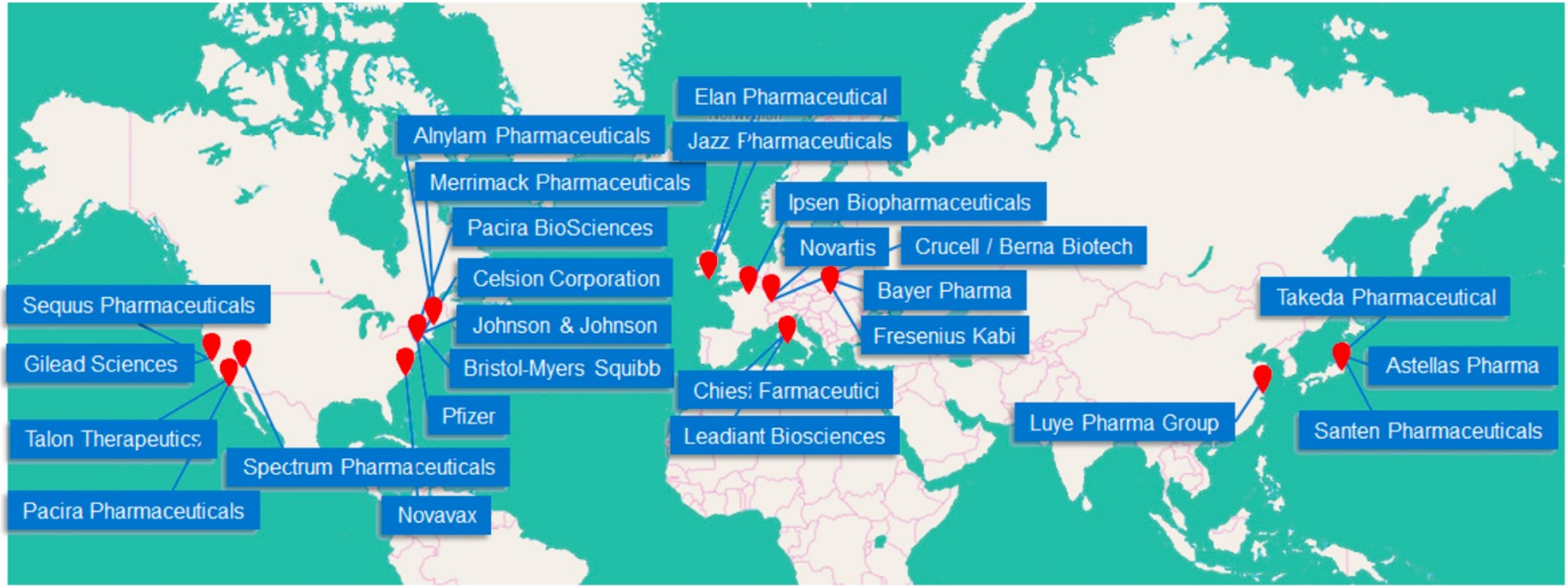


The continuous success of these LNPs for various disease treatment has demonstrated their enormous potential as the next-generation drug delivery systems, evidenced by the exponential increase of publications from 1990s .

Publication numbers increased dramatically from 23 publications in 1996 to more than 3000 in 2020.

NANOSAFETY

Approved LNP drugs and the diseases they target



KEY PLAYERS

Key players operating in the global LNP drug delivery market according to a recent market analysis and the summary of the LNP- based marketed drugs

NANOSAFETY

Since LNPs are mainly composed of natural lipids, they have been considered pharmacologically inactive and minimally toxic.

For example, while cationic lipids offer great promise as carriers for the delivery of fragile compounds such as nucleic acids, some cationic lipids cause cytotoxicity.

In some cases, cationic lipids reduce mitosis in cells, form vacuoles in the cytoplasms of cells, and cause detrimental effects on key cellular proteins such as protein kinase C.

The cytotoxicity of cationic lipids depends on the structures of their hydrophilic head groups; amphiphiles with quaternary ammonium head groups are more toxic than those with tertiary amine head groups.

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CONCLUSIONS

"This is not the end, this is not even the beginning of the end, this is just perhaps the end of the beginning."

Winston S. Churchill