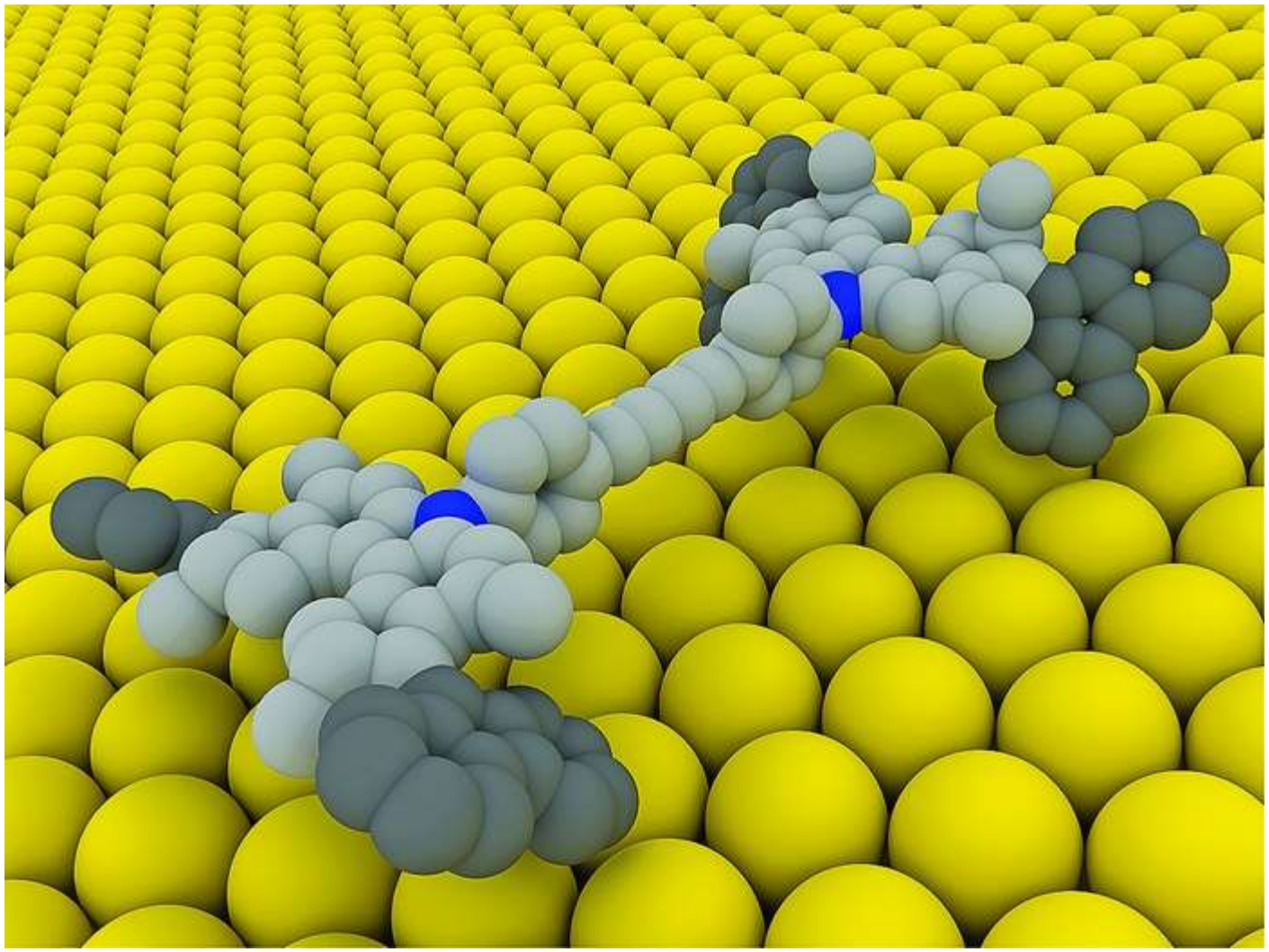
Nanobiotecnologia Curso 2018




ESTE UNIVERSO ES GIGANTESCO.
MENOS MAL QUE NOS ENCONTRAMOS, MADARIAGA.

Bionano, Nanobio…y todo eso

WIREs
NANOMEDICINE AND NANOBIOTECHNOLOGY

Nanotechnology is universally recognized as one of the most important scientific fields of the twenty-first century. Biomedical applications of this technology include nanobiotechnology and nanomedicine, one of seven emerging research areas highlighted by, and funded through, the NIH Roadmap for Medical Research. The advancement of this field relies on the combined efforts of researchers from many different backgrounds, including clinicians, biomedical engineers, materials scientists, applied physicists, and toxicologists. The need for a high-quality interdisciplinary review forum was pressing, and ***WIREs Nanomedicine and Nanobiotechnology*** looks to fill that niche. The topical coverage includes: Toxicology and regulatory issues; Implantable materials and surgical technologies; Diagnostic tools; Nanotechnology approaches to biology; Therapeutic approaches and drug discovery; Biology-inspired nanomaterials.

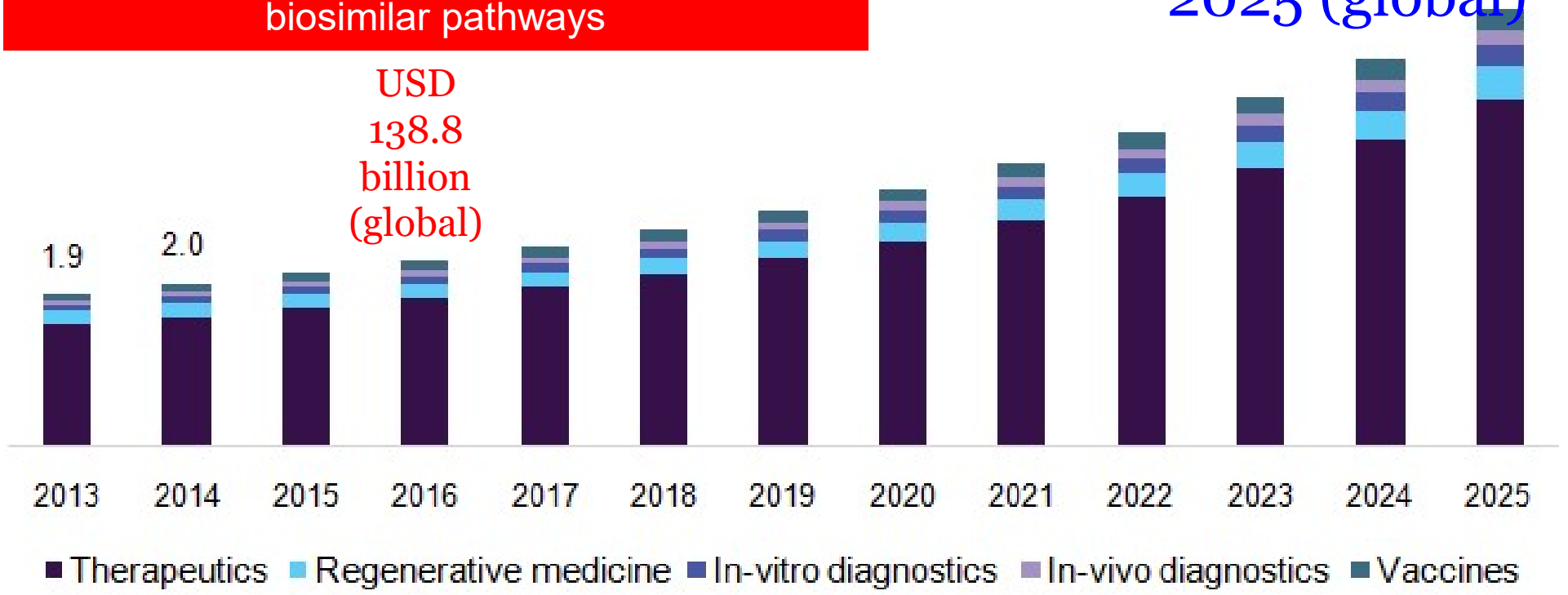
Nanobiotecnologia: situación de mercado

U.S. nanomedicine market by products, 2013 - 2025 (USD Billion)

The **global biologics market** generated a revenue of $**238.8 billion** in 2016. [monoclonal antibodies (MABs) and human insulin] biosimilar pathways

USD 350.8 billion by 2025 (global)

USD 138.8 billion (global)

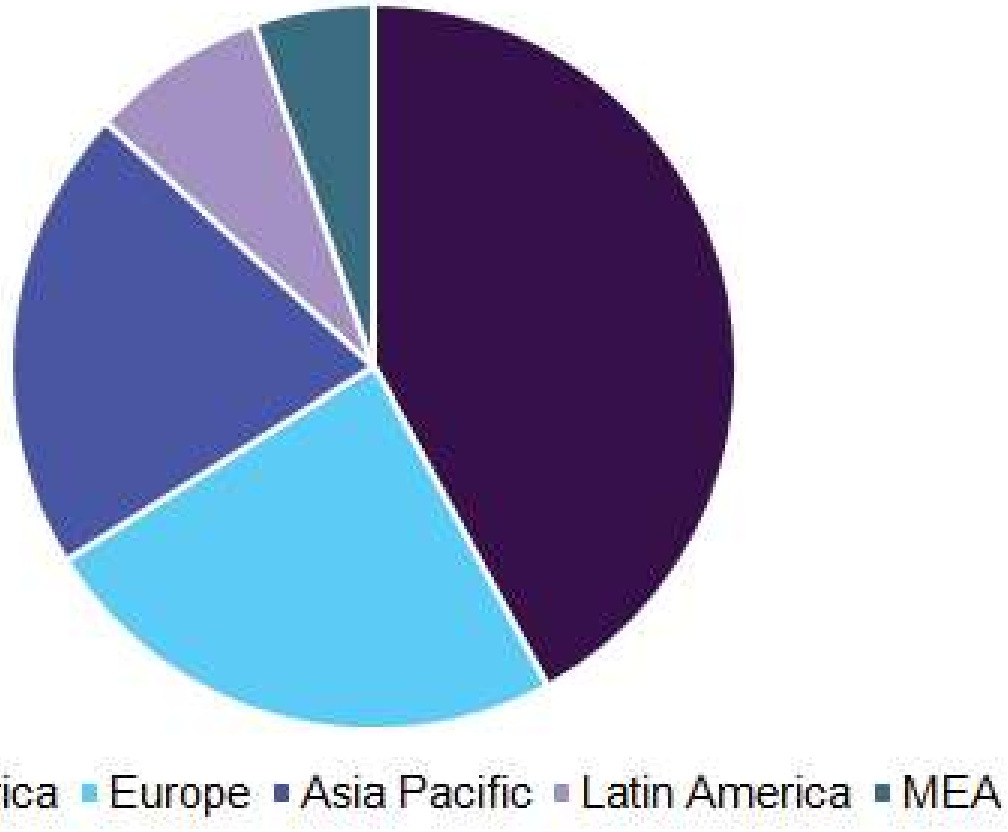


Clinical cardiology is expected to witness the fastest growth through to 2025 owing to development in nano-functionalization and modification of surfaces for increased biocompatibility of implants in treatment of late thrombosis

https://www.grandviewresearch.com/industry-analysis/nanomedicine-market

Nanomedicine market, by region, 2016 (%)

Asia Pacific is estimated to witness the fastest growth over the forecast period



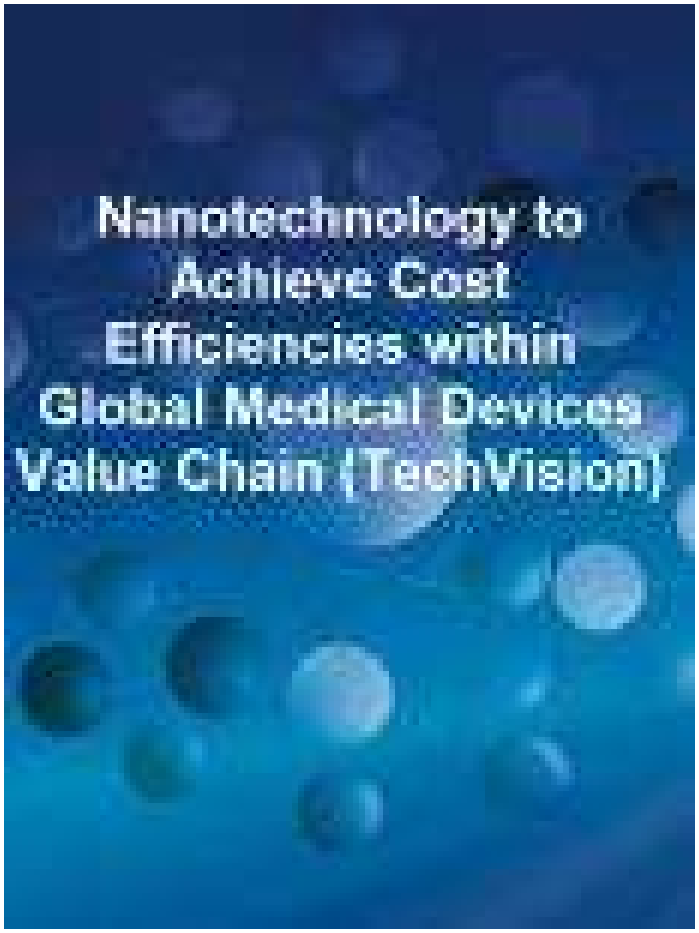
Factors responsible include government and regulatory authorities that have implemented a framework to encourage R&D collaborations and framework extension.

https://www.grandviewresearch.com/industry-analysis/nanomedicine-market

Las tendencias mas importantes presenciadas por este segmento del Mercado son la creciente demanda de tecnologia de *drug delivery*, mayor participación gubernamental en subsidios I+D, aparición de recientes desarrollos tecnologicos en el area de las nanomedicinas y mayores oportunidades de crecimiento/inversion.

Leading Companies
- Epeius Biotechnologies Corporation
- **Merck & Co Ltd**
- Teva Pharmaceutical Industries Ltd.
- **Abbott**
- **Johnson & Johnson Services, Inc**.
- Bio-Gate AG
- ABLYNX
- Brigham and Women's Hospital (BWH)
- Gilead
- CytImmune Sciences Inc
- Leadiant Biosciences, Inc.
- **Pfizer, Inc**
- Celgene Corporation
- AMAG Pharmaceuticals
- Nanospectra Biosciences, Inc.

https://www.businesswire.com/news/home/20171109006576/en/Global-Nanomedicine-Market-Analysis-Trends-2017-2025--



Development of nanotechnology-based medical devices enables major cost reduction across the medical device value chain, as it offers very high bargaining power to suppliers of medical device OEMs (original equipment manufacturers).

This research service (RS) analyzes the need for adoption of nanotechnologies in the medical devices industry, which are poised to enable creation of innovative medical device technologies that boost the overall quality of life for patients, and care providers. The RS evaluates the various technology developments within the major market segments within the global medical devices industry, such as drug delivery systems, in-vivo imaging, medical implants, and in-vitro diagnostics.

From a technology perspective, the research services covers an in-depth analysis of commercial applications of nanoscale materials, nanocoatings, biomimicking materials, nano-oncology applications, and development of nano-based surgical tools.

https://www.researchandmarkets.com/reports/3952444/nanotechnology-to-achieve-cost-efficiencies#relb1 2016

Nanobiotecnologia: productos y técnicas

FDA-approved nanomaterial-based drugs 2018

Name and type of nanomaterial	Year of approval or disease	Nature of nanomaterial	Mechanism of delivery and targeting
Doxil® (liposome)	1995 AIDS/Karposi's sarcoma 2005 ovarian cancer 2008 multiple myeloma	Doxorubicin hydrochloride encapsulated in PEGylated stealth liposome (100 nm)	Accumulation of liposome by passive targeting
Abelcet® (lipid–drug conjugate)	1995 fungal infections	1:1 complex of Amphotericin B with DMPC and DMPG (7:3), ribbon-like structures of a bilayered membrane	Reduce the toxicity of Amphotericin B
DaunoXome® (liposome)	1996 AIDS/Karposi's sarcoma	Liposome encapsulating daunorubicin citrate (45 nm)	Accumulation of liposome by passive targeting and sustained release of daunorubicin
Copaxone® (polymer conjugate)	1996 multiple sclerosis	Random copolymer of L-lysine, L-tyrosine, L-alanine and L-glutamate	Polymer with controlled molecular weight, clearance characteristics and owing to resemblance to myelin it 'decoys' an autoimmune response
AmBisome® (liposome)	1997 systemic fungal infections	Liposome encapsulating Amphotericin B (60–70 nm)	Selective release of the drug from liposome to fungal cell with minimal cellular uptake
DepoCyt® (liposome)	1999, 2007 lymphomatous malignant meningitis	Liposome encapsulating cytarabine	Releases the drug into the cerebral spinal fluid which results in extended half-life and prolonged exposure and drug retention
Visudyne® (liposome)	2000 age-related macular degeneration	Liposome encapsulating verteporfin	Supports the absorption of verteporfin to lipoproteins that carry it to the eyes where it is activated by shining light
Venofer® (magnetic)	2000 iron deficiency in chronic kidney disease	Complex of polynuclear iron (III)-hydroxide in sucrose	Increased and prolonged dosage
Renagel® (polymer conjugate)	2000 chronic kidney disease	Poly(allylamine hydrochloride) crosslinked with epichlorohydrin	Binds to dietary phosphate and prevents its absorption
PegIntron® (polymer conjugate)	2001 hepatitis C	PEG-conjugated IFNα-2β protein	PEG covalent conjugation increases the drug hydrodynamic radius and retention time without effecting the target site of protein

Agrahari,Vibhuti, Agrahari,Vivek, Facilitating the translation of nanomedicines to a clinical product: challenges and opportunities.Drug Discovery Today https://doi.org/10.1016/j.drudis.2018.01.047

FDA-approved nanomaterial-based drugs 2018 (cont)

Pegasys® (polymer conjugate)	2002 hepatitis B and C	PEG-conjugated IFNα-2β protein	PEG covalent conjugation increases the drug hydrodynamic radius and retention time without effecting the target site of protein
Neulasta® (polymer conjugate)	2002 febrile neutropenia, nonmyeloid malignancies, prophylaxis	PEG-conjugated filgrastim (granulocyte colony-stimulating factor)	PEG covalent conjugation increases the drug hydrodynamic radius and retention time without effecting the target site of protein
Eligard® (polymer conjugate)	2002 prostate cancer	Leuprolide acetate incorporated in nanoparticles of PLGH copolymer (DL-lactide/glycolide)	Controlled delivery of payload with longer circulation time
Somavert® (polymer conjugate)	2003 acromegaly	PEG-conjugated pegvisomant for injection, an analog of human growth hormone	PEG covalent conjugation increases the stability of GH receptor antagonist
Macugen® (polymer conjugate)	2004 age-related macular and neovascular degeneration	PEG-conjugated antivascular endothelial growth factor aptamer	PEG covalent conjugation increases the drug hydrodynamic radius and retention time without effecting the target site of protein
DepoDur® (liposome)	2004 for treatment of chronic pain	Morphine sulfate encapsulated in multivesicular liposomes (~20 μm)	Sustained release post administration in the epidural
Abraxane® (polymer–drug conjugate)	2005 metastatic breast cancer 2012 metastatic non-small-cell lung cancer 2013 metastatic adenocarcinoma of the pancreas	Albumin-conjugated with paclitaxel to form 130 nm particle	Hydrophobic molecules and help endothelial transcytosis of protein-bound and unbound plasma constituents through binding to the cell surface
Mircera® (polymer conjugate)	2007 anemia associated with chronic renal failure in adults	PEG-conjugated erythropoietin receptor activator	PEG covalent conjugation increases the drug hydrodynamic radius and retention time without effecting the target site of protein
Cimzia® (polymer conjugate)	2008 Crohn's disease 2009 rheumatoid arthritis 2012 psoriatic arthritis 2013 ankylosing spondylitis	PEG-conjugated tumor necrosis factor (TNF)-α inhibitor (certolizumab)	PEG covalent conjugation increases the drug hydrodynamic radius and retention time without effecting the target site of protein

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FDA-approved nanomaterial-based drugs 2018 (cont)

Feraheme™ (magnetic)	2009 deficiency anemia and iron deficiency in chronic kidney disease	Ferumoxytol SPION with polyglucose sorbitol carboxymethylether	Polymeric coating allows sustained release of Fe^{2+}, decreasing number of doses
Marqibo® (liposome)	2012 acute lymphoblastic leukemia	Liposome encapsulating vincristine sulfate (100 nm)	Enhanced efficacy and reduced toxicity of bare drug
Plegridy® (polymer conjugate)	2014 multple sclerosis	PEG-conjugated IFNβ-1α	PEG covalent conjugation increases the drug hydrodynamic radius and retention time without effecting the target site of protein
Onivyde® (liposome)	2015 pancreatic cancer	PEG-conjugated liposome nanoparticle encapsulating Irinotecan	Enhanced efficacy, improved circulation time which allows accumulation in tumor site by EPR and reduced toxicity of bare drug
Adynovate® (polymer conjugate)	2015 hemophilia	PEG-conjugated antihemophilic factor (recombinant)	PEG covalent conjugation increases the drug hydrodynamic radius and retention time without effecting the target site of protein
Genexol® PM	Breast cancer, non-small-cell lung cancer, ovarian cancer	Polymeric-micelle-formulated paclitaxel consisting of PEG and poly(D,L-lactic acid) (PDLLA), and free of Cremophor® EL	Stabilization of microtubules, thus preventing cell division
Myocet® (liposome)	2000 (in Europe and Canada) breast neoplasms	Non-PEGylated liposome-encapsulated doxorubicin–citrate complex corresponding to 50 mg doxorubicin hydrochloride	Works by interfering with the DNA within cells, preventing them from making more copies of DNA and making proteins. This means that cancer cells cannot divide and eventually die

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(nano) medicina

Nanotherapeutics in active clinical trials (not yet recruiting, recruiting, or active) grouped by the drug being deli... rce: www clinicaltrials.gov.

Product name	Delivery vehicle	Drug	Clini...	Phase
JVRS-100	Liposomes	Plasmid DNA		
SGT-53	Liposomes	DNA		
NU-0129	Nucleic acid-coated gold nanoparticles	DNA		
PNT2258	Lipid nanoparticles	DNA		
siRNA-EphA2-DOPC	Liposomes	siRNA		
DCR-PH1	Lipid nanoparticles			
STP705	Polymeric nanoparticles			
ALN-TTR02	Lipid nanoparticles			III
				III
				III
Lipo-MERIT	Lipoplex	m		I
TNBC-MERIT	Lipoplex	mR	16457	I
mRNA-1325	Lipid nanoparticles	mRN	CT03014089	I/II
BP1001	Liposomes	Antise	NCT01159028	I
			NCT02781883	II
			NCT02923986	I/II
			NCT02340156	II
			NCT02340117	II
ARB-001467	Lipid nanoparticles	RNAi triggers	NCT02631096	II
L-BLP25	Liposomes	Peptide	NCT01462513	II
MAG-TN3 + AS15	Liposomes	Peptide	NCT02364492	I

Biologics: monoclonal antibody (mAbs), hormones, growth factors, fusion proteins, cytokines, therapeutic enzymes, vaccines, blood factors, and anticoagulants. The mAbs are the dominating other types in terms of sales and therapeutic enzymes is the highest growing type.

Macromolecule nanotherapeutics: approaches and challenges Puneet Tyagi Q1 z and Jose Luis SantosDrug Discovery Today Volume 00, Number 00 January 2018

Técnicas analíticas empleadas en la caracterización estructural de nanomateriales

Techniques	Physicochemical characteristics analyzed	Strengths	Limitations
Dynamic light scattering (DLS)	• Hydrodynamic size distribution	• Nondestructive/invasive manner • Rapid and more-reproducible measurement • Measures in any liquid media, solvent of interest • Hydrodynamic sizes accurately determined for monodisperse samples • Modest cost of apparatus	• Insensitive correlation of size fractions with a specific composition • Influence of small numbers of large particles • Limit in polydisperse sample measures • Limited size resolution • Assumption of spherical shape samples
Fluorescence correlation spectroscopy (FCS)	• Hydrodynamic dimension • Binding kinetics	• High spatial and temporal resolution • Low sample consumption • Specificity for fluorescent probes • Method for studying chemical kinetics, molecular diffusion, concentration effect and conformation dynamics	• Limit in fluorophore species • Limited applications and inaccuracy owing to lack of appropriate models
Zeta potential	• Stability • Referring to surface charge	• Simultaneous measurement of many particles (using ELS)	• Electro-osmotic effect • Lack of precise and repeatable measurement
Raman scattering (RS) Surface enhanced Raman scattering (SERS) Tip-enhanced Raman spectroscopy (TERS)	• Hydrodynamic size and size distribution (indirect analysis) • Conformation change of protein–metallic-NP conjugate • Structural, chemical and electronic properties	• Complementary data to IR • No requirement of sample preparation • Potential of detecting tissue abnormality • Enhanced RS signal (SERS) • Increased spatial resolution (SERS) • Topological information of nanomaterials (SERS, TERS)	• Relatively weak single compared to Rayleigh scattering • Limited spatial resolution (only to μm) • Extremely small cross-section • Interference of fluorescence • Irreproducible measurement (SERS)

Agrahari,Vibhuti, Agrahari,Vivek, Facilitating the translation of nanomedicines to a clinical product: challenges and opportunities.Drug Discovery Today https://doi.org/10.1016/j.drudis.2018.01.047

Técnicas analíticas empleadas en la caracterización estructural de nanomaterials (cont)

Near-field scanning optical microscopy (NSOM)	• Size and shape of nanomaterials	• Simultaneous fluorescence and spectroscopy measurement • Nanoscaled surface analysis at ambient conditions • Assessment of chemical information and interactions at nanoscaled resolution	• Long scanning time, small specimen area analyzed • Incident light intensity insufficient to excite weak fluorescent molecules • Difficulty in imaging soft materials • Analysis limited to the nanomaterial surface
Circular dichroism (CD)	• Structure and conformational change of biomolecules (e.g., protein and DNA) • Thermal stability	• Nondestructive and prompt technique	• Nonspecificity of residues involved in conformational change • Less sensitive than absorption methods • Weak CD signal for nonchiral chromophores • Challenging for analysis of molecules containing multiple chiral chromophores
Mass spectroscopy (MS)	• Molecular weight • Composition structure • Surface properties (secondary ion MS)	• High accuracy and precision in measurement • High sensitivity to detection (a very small amount of sample required)	• Expensive equipment • Lack of complete databases for identification of molecular species • Limited application to date in studying nanomaterial bioconjugates
Infrared spectroscopy (IR) Attenuated total reflection Fourier transform infrared (ATR-FTIR)	• Structure and conformation of bioconjugate • Surface properties (ATR-FTIR)	• Fast and inexpensive measurement • Minimal or no sample preparation requirement (ATR-FTIR) • Improving reproducibility (ATR-FTIR) • Independence of sample thickness (ATR-FTIR)	• Complicated sample preparation (IR) • Interference and strong absorbance of H_2O (IR) • Relatively low sensitivity in nanoscale analysis
Scanning electron microscopy (SEM) Environmental SEM (ESEM)	• Size and size distribution • Shape • Aggregation • Dispersion	• Direct measurement of the size and size distribution and shape of nanomaterials • High resolution (down to subnanometer)	• Conducting sample or coating conductive materials required • Dry samples required, sample analysis in nonphysiological

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Técnicas analíticas empleadas en la caracterización estructural de nanomaterials (cont)

		• Images of biomolecules in natural state provided using ESEM	conditions (except ESEM) • Biased statistics of size distribution in heterogeneous samples • Expensive equipment • Cryogenic method required for most NP bioconjugates • Reduced resolution in ESEM
Transmission electron microscopy (TEM)	• Size and size distribution • Shape heterogeneity • Aggregation • Dispersion	• Direct measurement of the size and size distribution and shape of nanomaterials with higher spatial resolution than SEM • Several analytical methods coupled with TEM for investigation of electronic structure and chemical composition of nanomaterials	• Ultrathin samples in required • Samples in nonphysiological condition • Sample damage or alternation • Poor sampling • Expensive equipment
Scanning tunneling microscopy (STM)	• Size and size distribution • Shape • Structure • Dispersion • Aggregation	• Direct measurement • High spatial resolution at atomic scale	• Conductive surface required • Surface electronic structure and surface topography unnecessarily having a simple connection
Atomic force microscopy (AFM)	• Size and size distribution • Shape • Structure • Sorption • Dispersion • Aggregation • Surface properties (modified AFM)	• 3D sample surface mapping • Subnanoscaled topographic resolution • Direct measurement of samples in dry, aqueous or ambient environment	• Overestimation of lateral dimensions • Poor sampling and time consuming • Analysis in general limited to the exterior of nanomaterials
Nuclear magnetic resonance (NMR)	• Size (indirect analysis) • Structure • Composition • Purity • Conformational change	• Nondestructive or noninvasive method • Little sample preparation	• Low sensitivity • Time consuming • Relatively large amount of sample required • Only certain nuclei NMR active

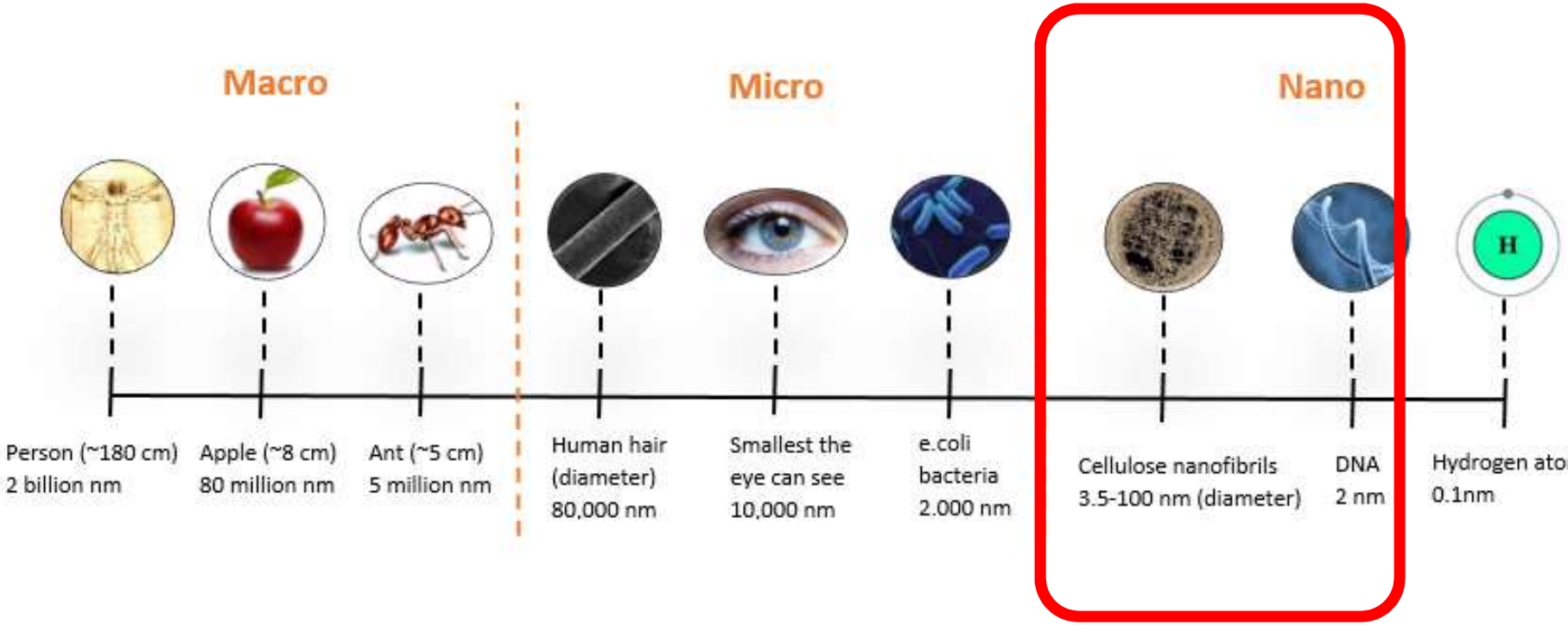
Agrahari,Vibhuti, Agrahari,Vivek, Facilitating the translation of nanomedicines to a clinical product: challenges and opportunities.Drug Discovery Today https://doi.org/10.1016/j.drudis.2018.01.047

Técnicas analíticas empleadas en la caracterización estructural de nanomaterials (cont)

X-ray diffraction (XRD)	• Size, shape and structure for crystalline materials	• Well-established technique • High spatial resolution at atomic scale	• Limited applications in crystalline materials • Only single conformation/binding state of sample accessible • Low intensity compared to electron diffraction
Small-angle X-ray scattering (SAXS)	• Size and size distribution • Shape • Structure	• Nondestructive method, simplification of sample preparation • Amorphous materials and sample in solution accessible	• Relatively low resolution

Agrahari,Vibhuti, Agrahari,Vivek, Facilitating the translation of nanomedicines to a clinical product: challenges and opportunities.Drug Discovery Today https://doi.org/10.1016/j.drudis.2018.01.047

Nanobiotecnologia: nuevas propiedades materiales



nanoescala:200/300-1 nm

1 nm= 10^{-9} m

En la **nanoescala** ocurren nuevos fenómenos físicos y biológicos:

Computer simulation of electron motions within a nanowire that has a diameter in the nanoscale range.

http://www.nano.gov/nanotech-101/special

Propiedades de la nanoescala 1: ↑↑↑↑ área/volumen

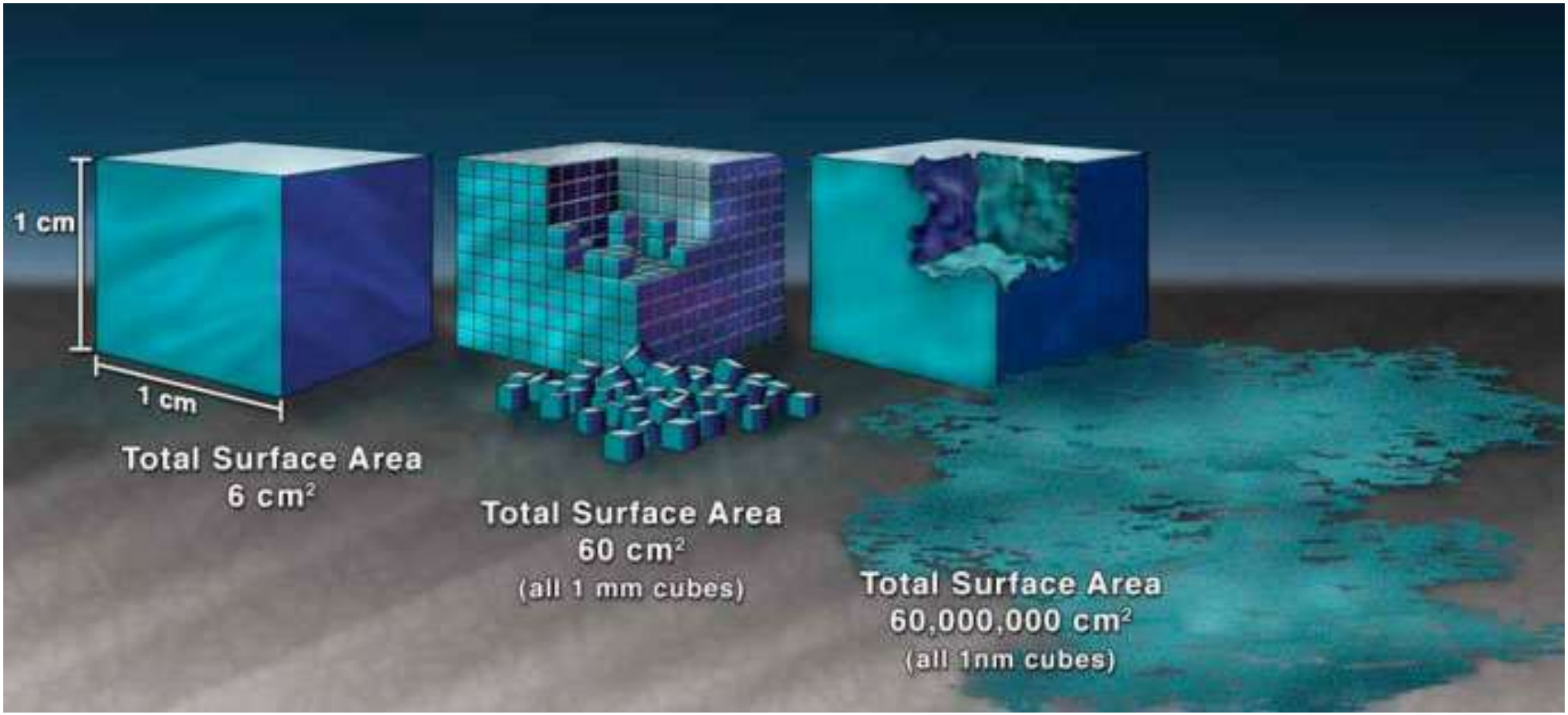


Illustration demonstrating the effect of the increased surface area provided by nanostructured materials

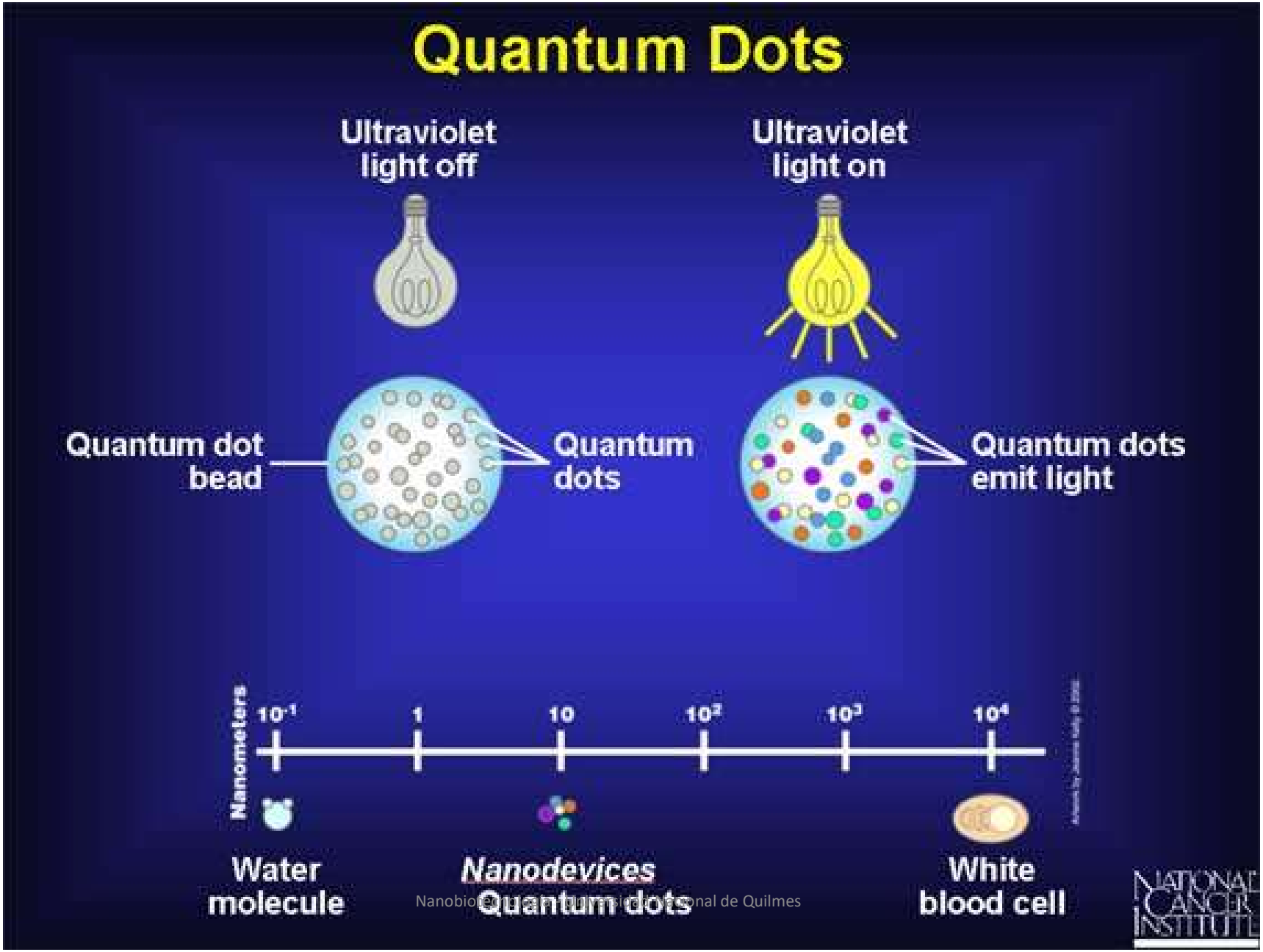
http://www.nano.gov/nanotech-101/special

Propiedades de la nanoescala 2: nuevos fenómenos cuanticos

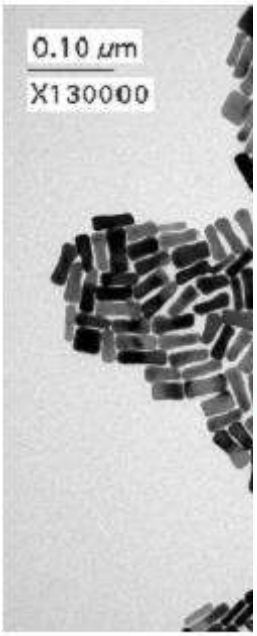
¡¡Cambio en las propiedades **intensivas** (punto de fusión, fluorescencia, conductividad eléctrica, permeabilidad magnética, reactividad química **en función del tamaño!!**

Nanoparticulas de oro (Au)

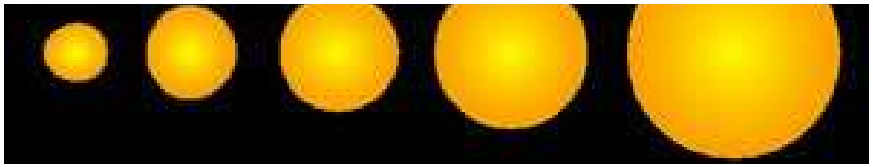
http://www.nano.gov/nanotech-101/special



Propiedades de la nanoescala 2: el color depende del tamaño y forma



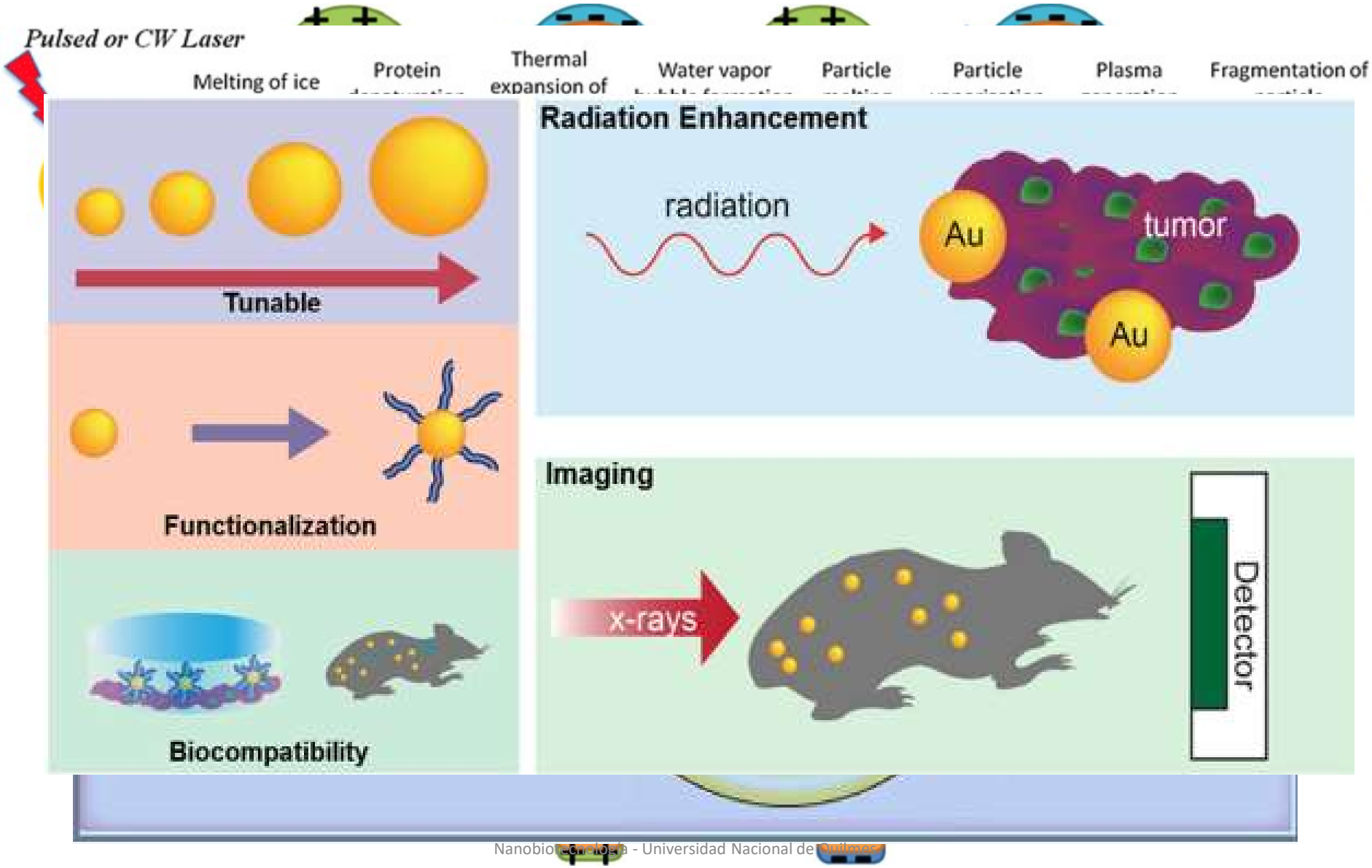
nP. Oro (nm)		nP. Plata (nm)	
	- Ø = 25 - Esfera - Rojo	- Ø = 100 - Esfera - Amarillo	
	- Ø = 50 - Esfera - Verde	- Ø = 40 - Esfera - Azul	
	- Ø = 100 - Esfera - Naranja	- Ø = 100 - Prisma - Rojo	
Oro en masa	amarillo	Color plata	Plata en masa



5 nm

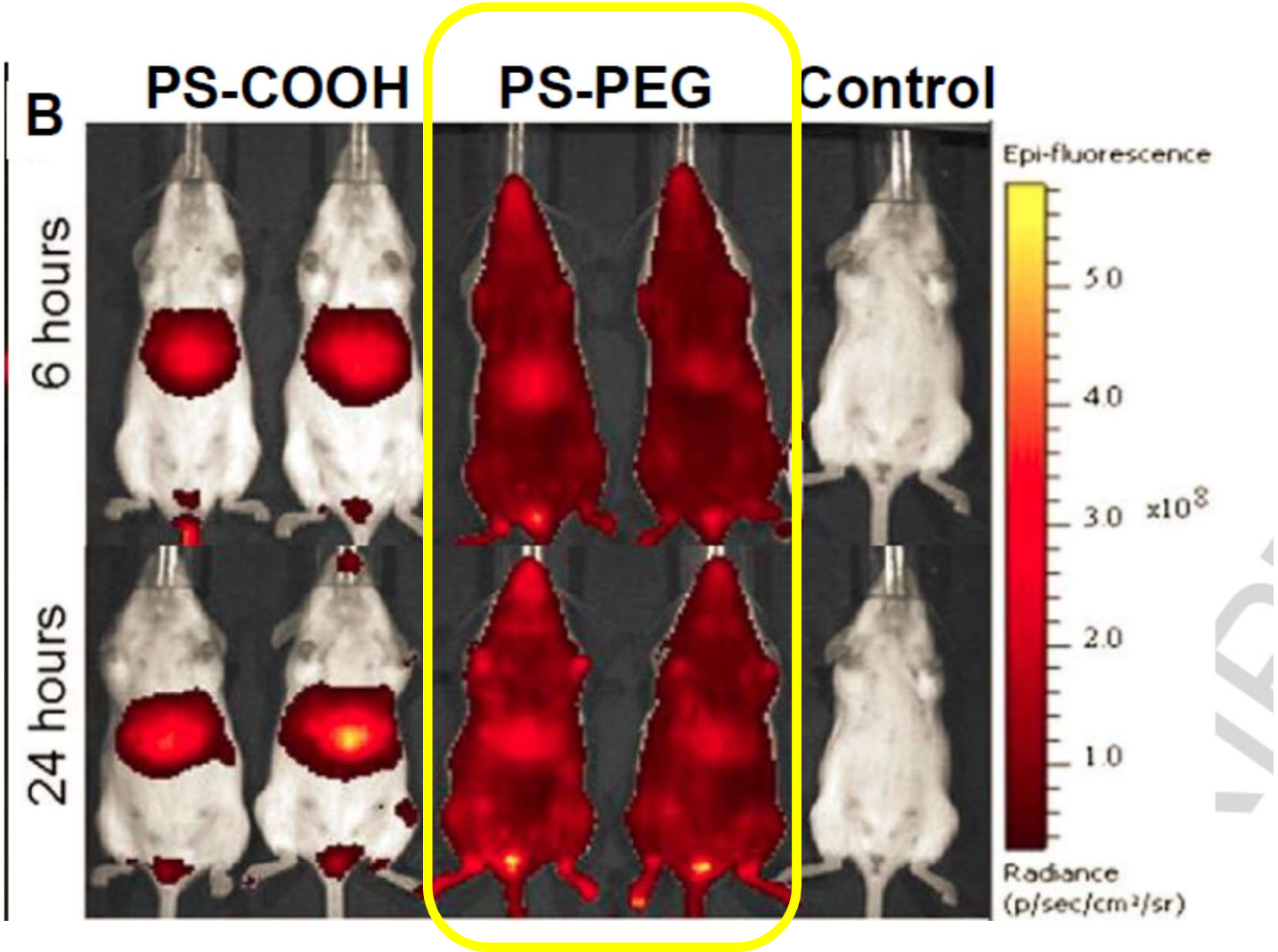
90 nm

Propiedades de la nanoescala 2: nuevos fenómenos cuánticos: SPR Surface Plasmon Resonance



Efecto de la peguilacion

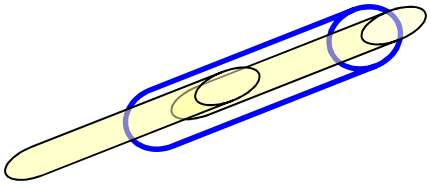
Jung Soo Suk, Qingguo Xu, Namho Kim, Justin Hanes, Laura M. Ensign, PEGylation as a strategy for improving nanoparticle-based drug and gene delivery, *Advanced Drug Delivery Reviews* (2015),



(B) PS-PEG NPs remained in systemic circulation, whereas uncoated PS-COOH NPs accumulate in the liver.

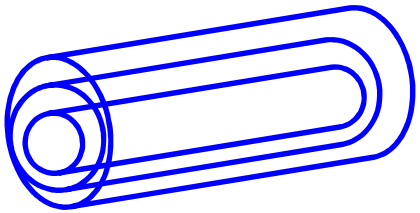
Nanotubos de carbono

Láminas de grafeno (sp^2) que se enrollan sobre si mismas



SWCNT TEM MWCNT

monopared multipared



Gran AREA SUPERFICIAL SWCNT:

1000 m^2/g

(C_{black} (micromaterial) 60-80 m^2/g)

Gran RELACION DE ASPECTO (> 100)

ESTABILIDAD MECÁNICA Y TÉRMICA

EXCELENTES CONDUCTORES TÈRMICOS y electricos (A LO LARGO DEL EJE: **BALISTICOS**)

AISLANTES ⊥ EJE

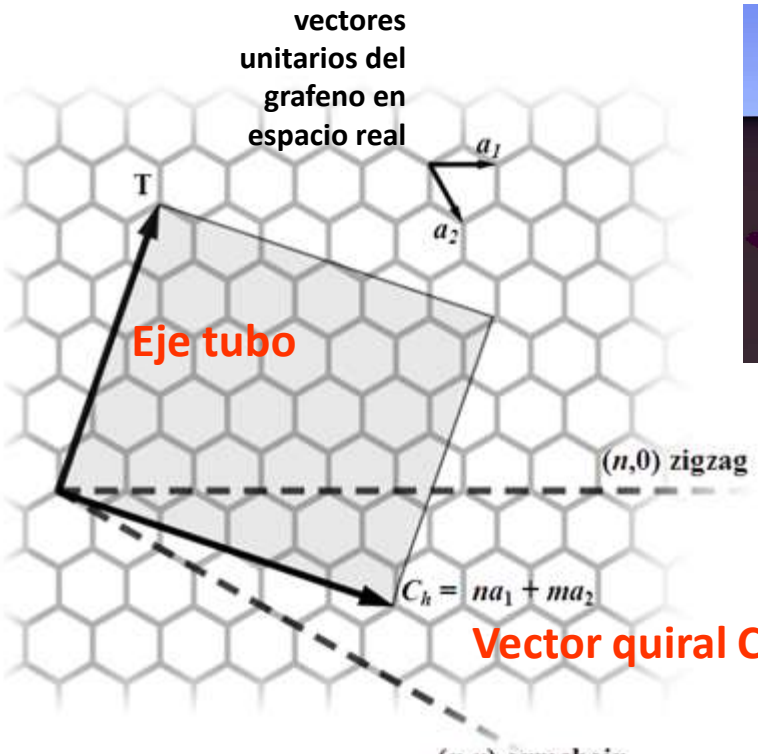
NANOCOMPOSITES ANISOTRÓPICOS

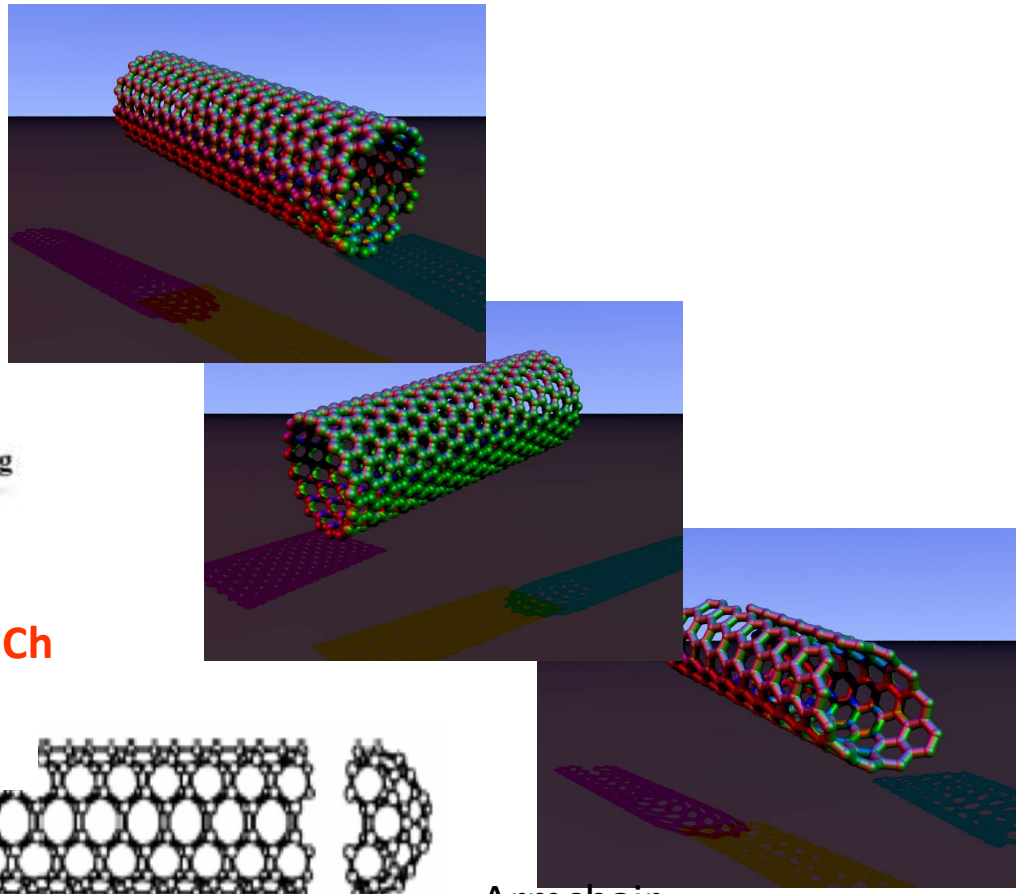
Biochimica et Biophysica Acta 1758 (2006) 404-412.
Funcionalized carbon nanotubes as emerging nanovectors for the delivery of therapeutics. Cedric Klumpp, Kostas Kostarelos, Maurizio Prato, Alberto Bianco.

NTC 1μm

Liposoma 100 nm

PAMAM G5





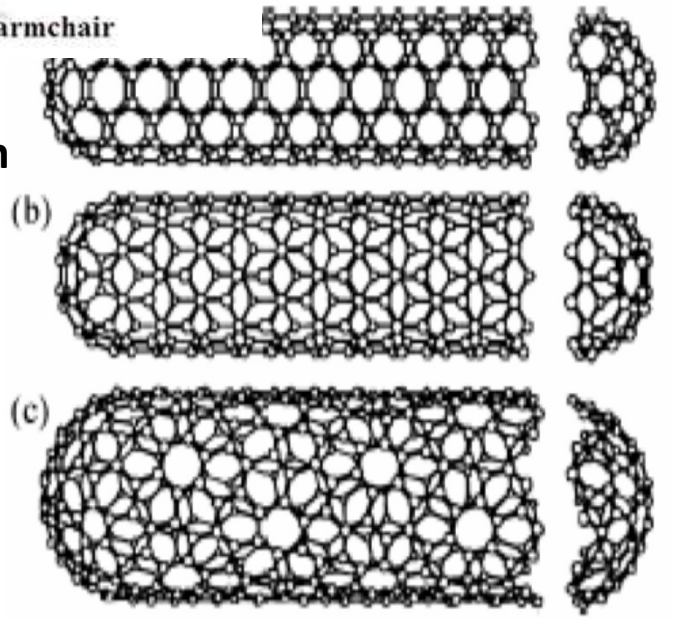
n: átomos C alrededor circunferencia del tubo

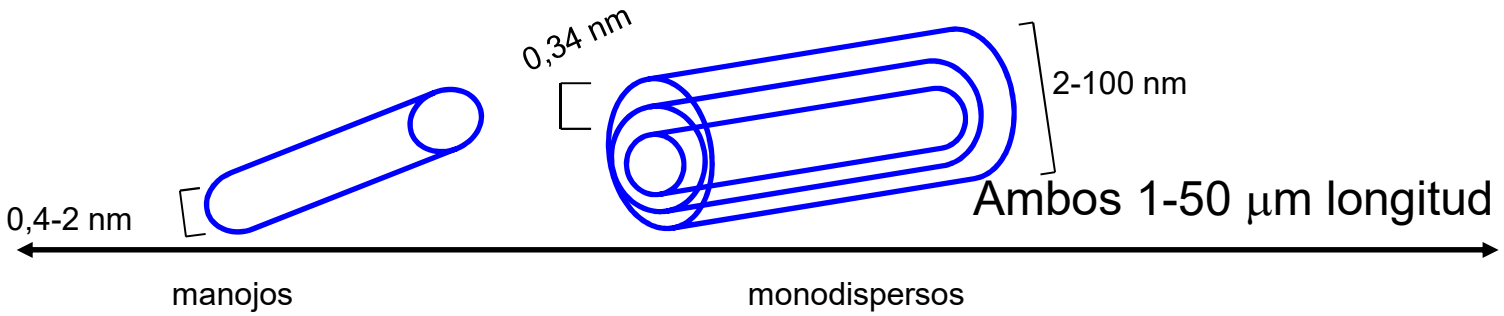
m: átomos C hacia el eje del tubo

n = m Armchair

n , 0 Zigzag

n, m Quiral





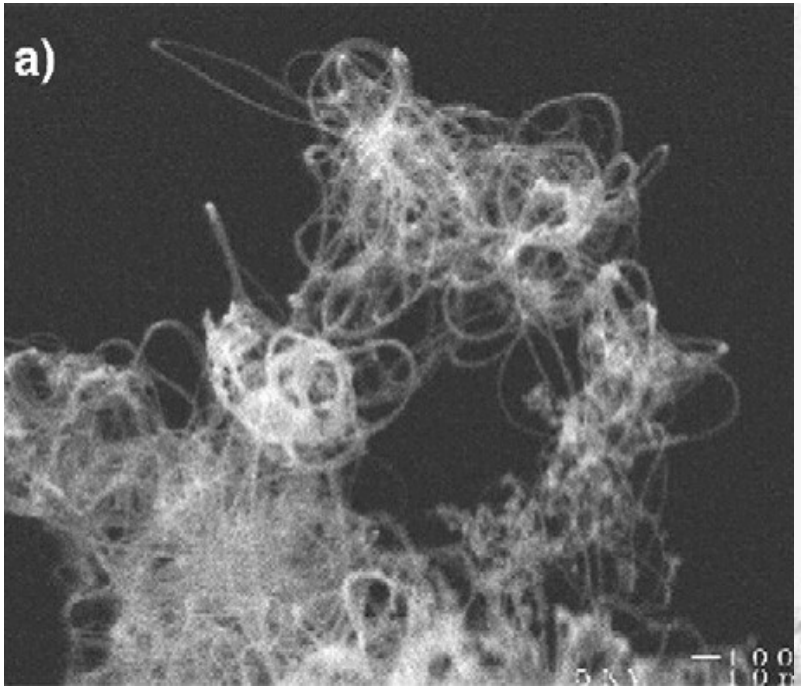
Extremos abiertos muy reactivos

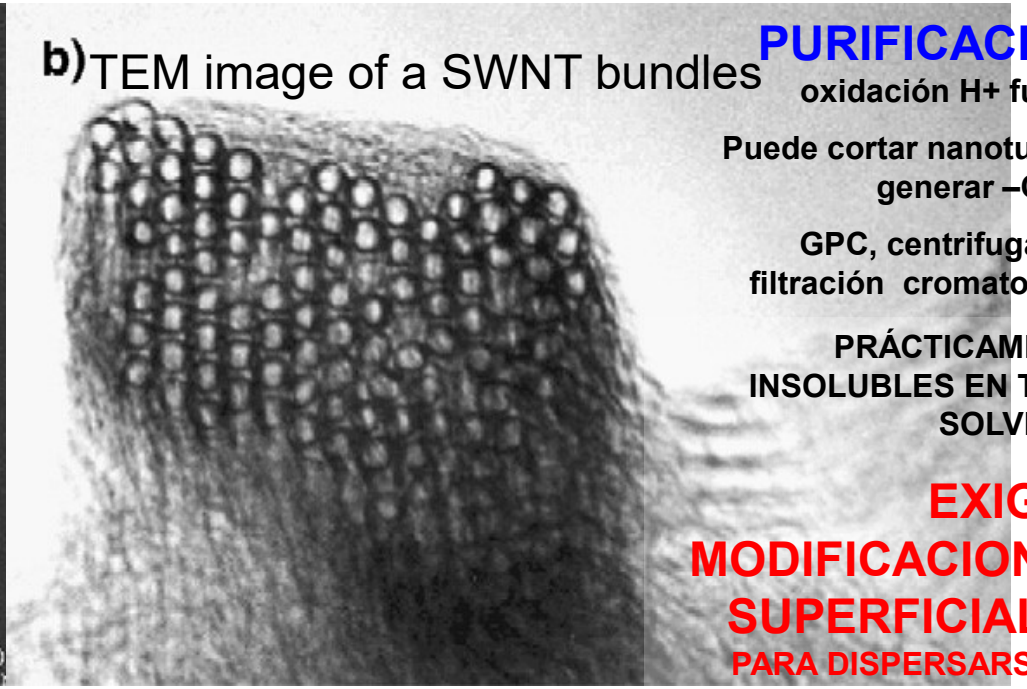
Extremos cerrados

MÉTODOS DE PREPARACIÓN: i) descarga de arco, ii) ablación láser

iii) deposición química de vapor: reacción de gas (acetileno, etileno, etanol) que contiene C junto a partículas metálicas catalíticas (Co, Ni, Fe) a T > 600 °C

HiPCO (high pressure CO conversion) fácilmente escalable, pocas impurezas (30 % Ni, Fe, C amorfo, nanopartículas residuales) obligatoriamente removidas





PURIFICACIÓN:

oxidación H+ fuertes

Puede cortar nanotubos y generar –COOH

GPC, centrifugación, filtración cromatografía

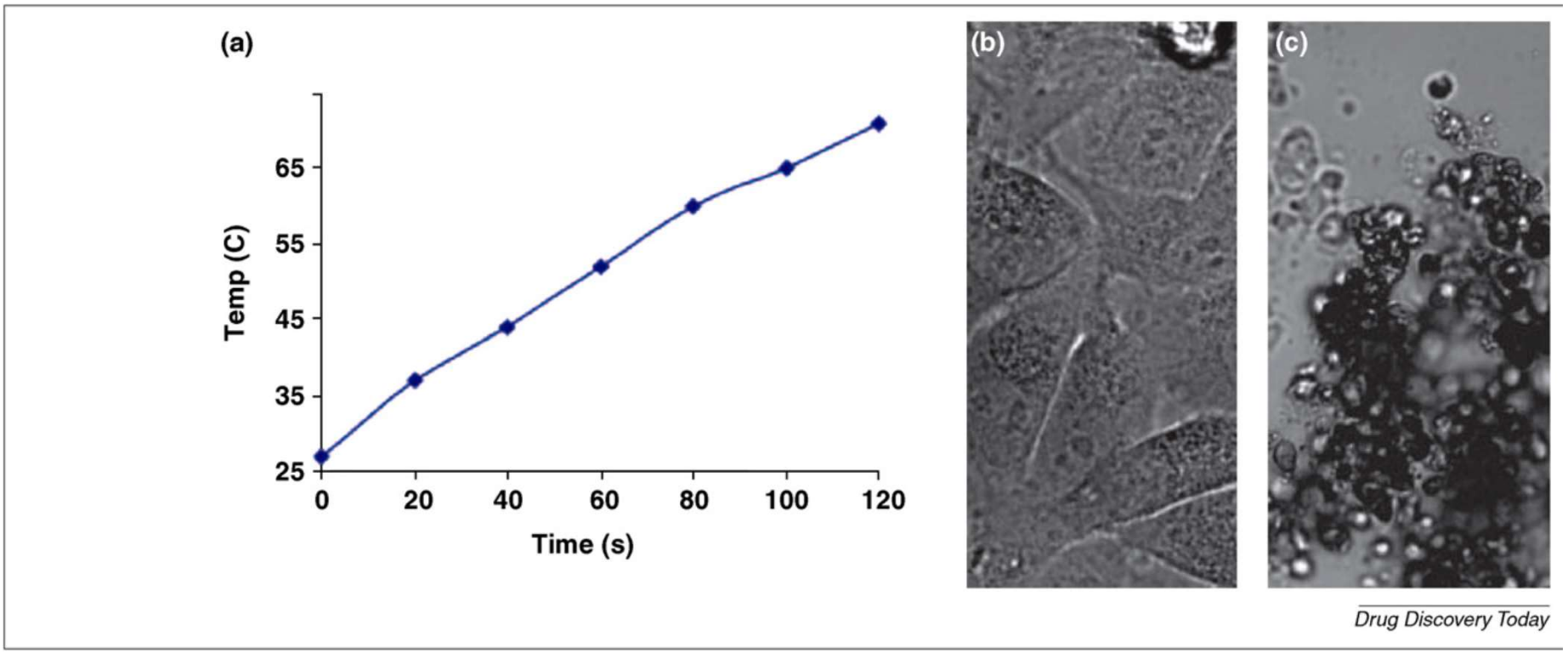
PRÁCTICAMENTE INSOLUBLES EN TODO SOLVENTE

EXIGEN MODIFICACIONES SUPERFICIALES

PARA DISPERSARSE EN SOLVENTES ACUOSOS

The role of surfactants in dispersion of carbon nanotubes Linda Vaisman , H. Daniel Wagner , Gad Marom Advances in Colloid and Interface Science 128–130 (2006) 37–46

Yi Zhang Yuhong Bai and Bing Yan Functionalized carbon nanotubes for potential medicinal applications Drug Discovery Today
Volume 15, Numbers 11/12 June 2010



Usos terapéuticos?

SWNT can absorb NIR radiation energy and cause local heating, which can lead to HeLa cell destruction. (a) Temperature evolution of a DNA-SWNT solution (approximately 25 mg/l) during continuous radiation by an 808 nm laser at 1.4 W/cm2 for two minutes. (b) Image of HeLa cells without internalized SWNTs after continuous 808 nm laser radiation at 3.5 W/cm2 for 5 min. No cell death was observed. (c) Image of dead and aggregated cells after internalization of DNA-SWNT and laser radiation at 1.4 W/cm2 for 2 min. The dead cells showed rounded and aggregated. Reproduced, with permission, from Ref. [49]. Copyright 2005 National Academy of Sciences, USA.

Pulmonary toxicity of carbon nanotubes: a systematic report Jitendra Kayat, MPharm, Virendra Gajbhiye, MPharm, Rakesh Kumar Tekade, MPharm, Narendra Kumar Jain, PhD⁎Nanomedicine: Nanotechnology, Biology, and Medicine xx (2010) xxx–xxx

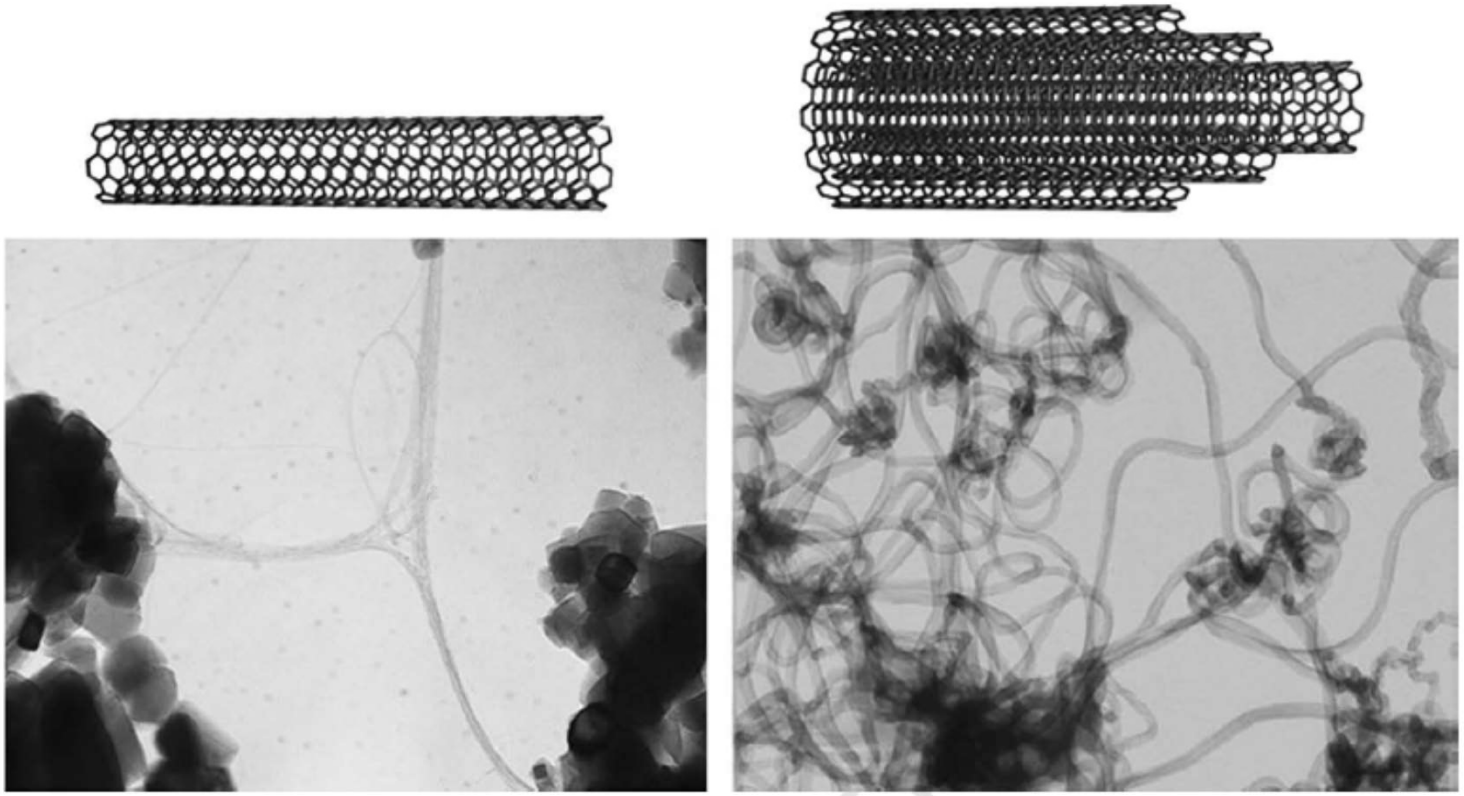
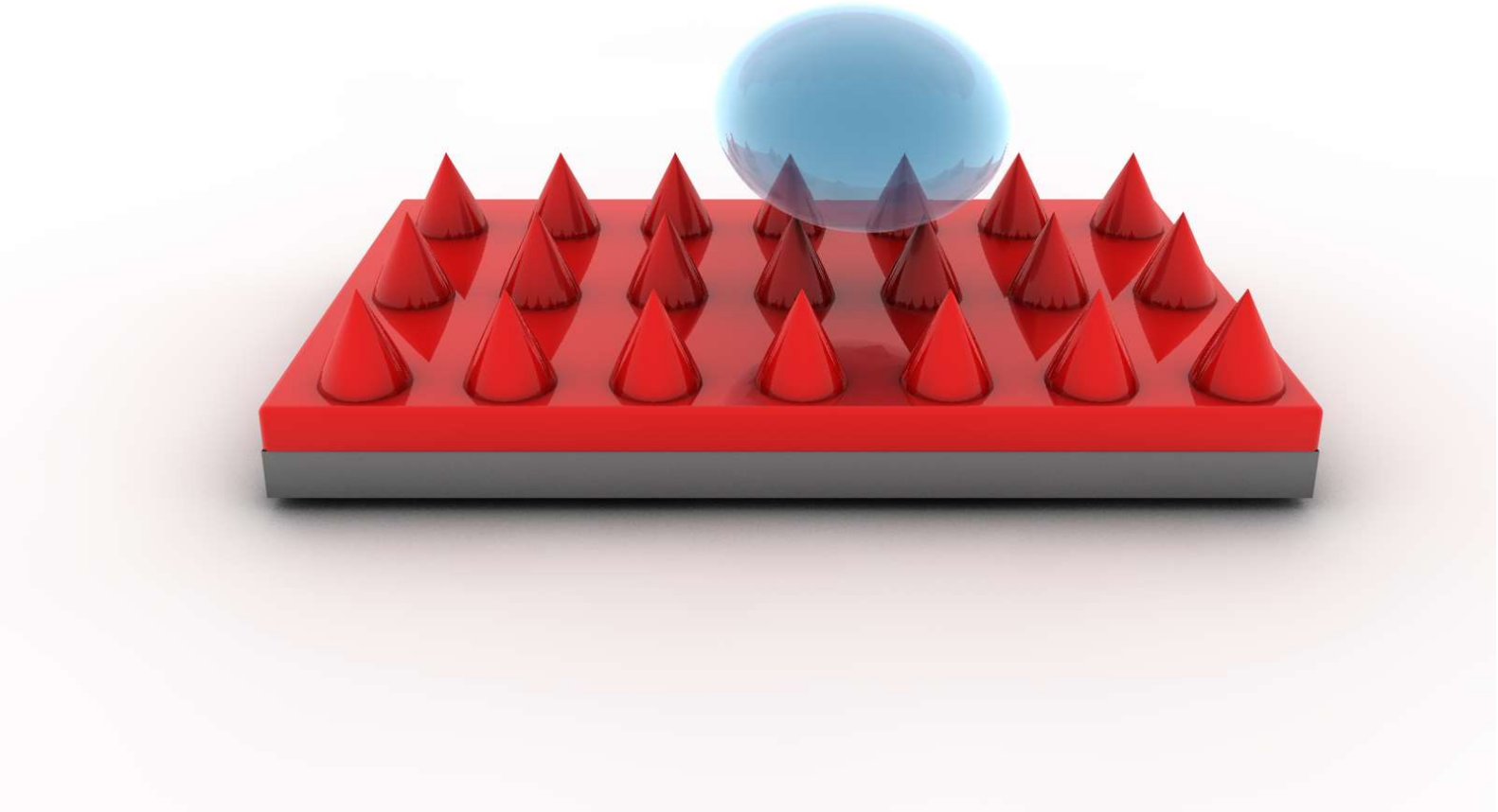


Figure 1. Basic types of CNTs SWCNTs (top left) and MWCNTs (top right) with typical transmission electron micrographs below. (Adapted from Donaldson et al[28] with permission from publisher – to be obtained.)

Control de la materia en la nanoescala (propiedades mnanoescala 3): efecto loto/superficies hidrofobicas



Vida diaria

Electrónica y TICs: dispositivos mas veloces, pequeños, portátiles, con mayor memoria y capacidades

gia

Nanotransistores

Magnetic random access memory (MRAM): salvado eficiente y veloz de datos encriptados frente a desconexion o accidentes.

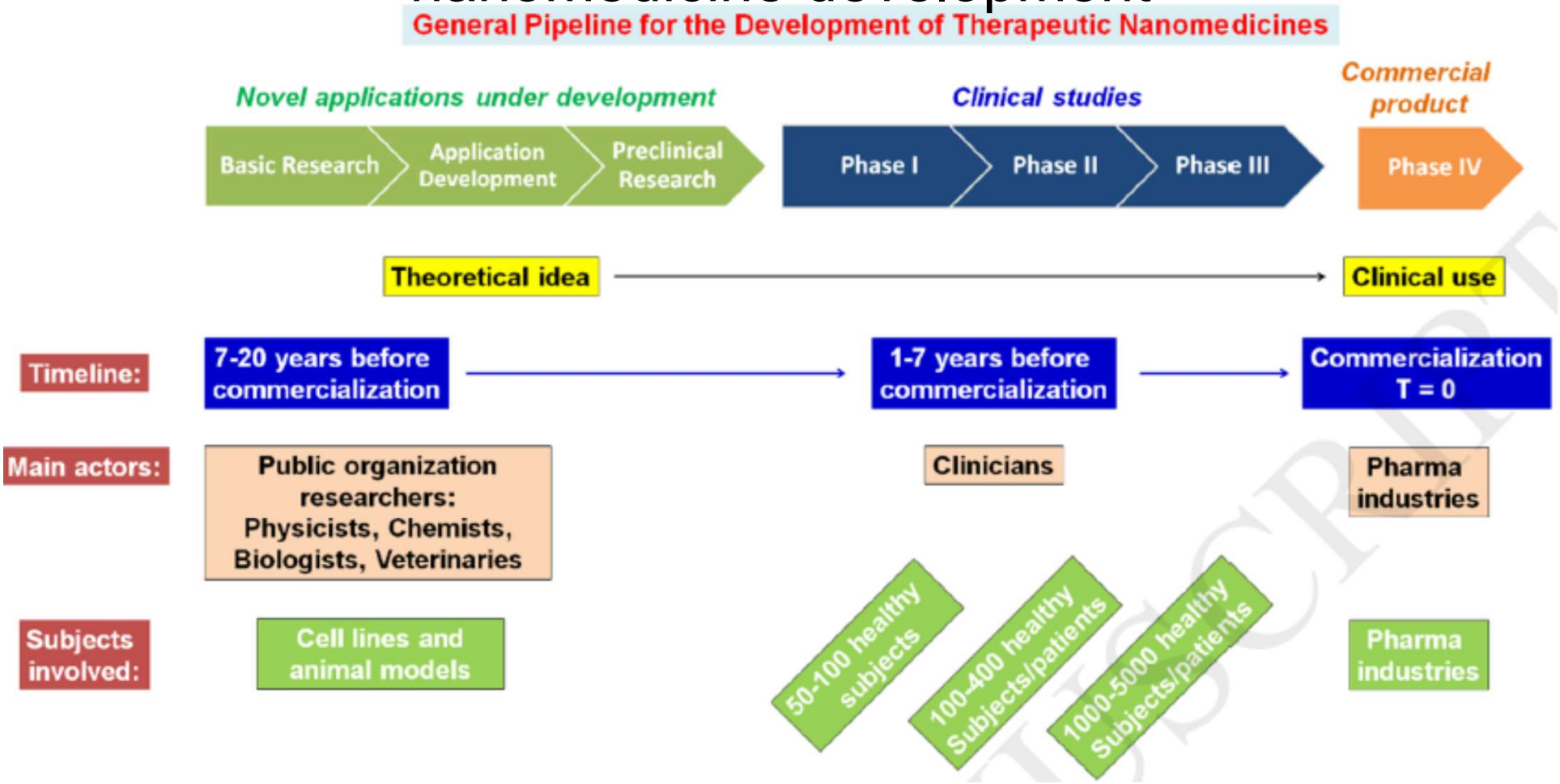
ambiental/filtros

Salud

RETOS a supercar en el desarrollo y comercializacion de productos nanomedicos/nanobiotecnologicos

Agrahari,Vibhuti, Agrahari,Vivek, Facilitating the translation of nanomedicines to a clinical product: challenges and opportunities.Drug Discovery Today https://doi.org/10.1016/j.drudis.2018.01.047

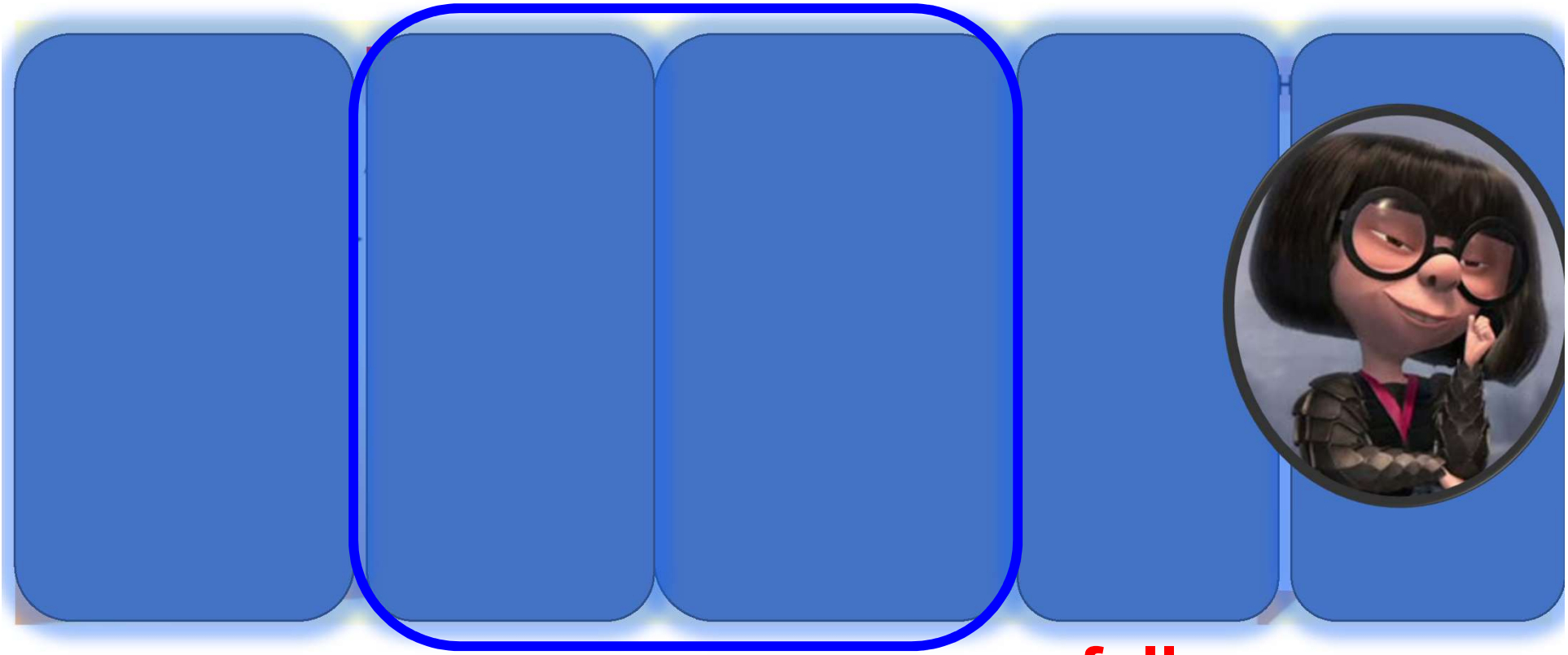
Schematic representation of the process of nanomedicine development



Agrahari,Vibhuti, Agrahari,Vivek, Facilitating the translation of nanomedicines to a clinical product: challenges and opportunities.Drug Discovery Today https://doi.org/10.1016/j.drudis.2018.01.047

Etapas en el desarrollo de medicamentos

Etapas Pre-clinicas | Etapas clínicas



falla **3D+3R** **falla**

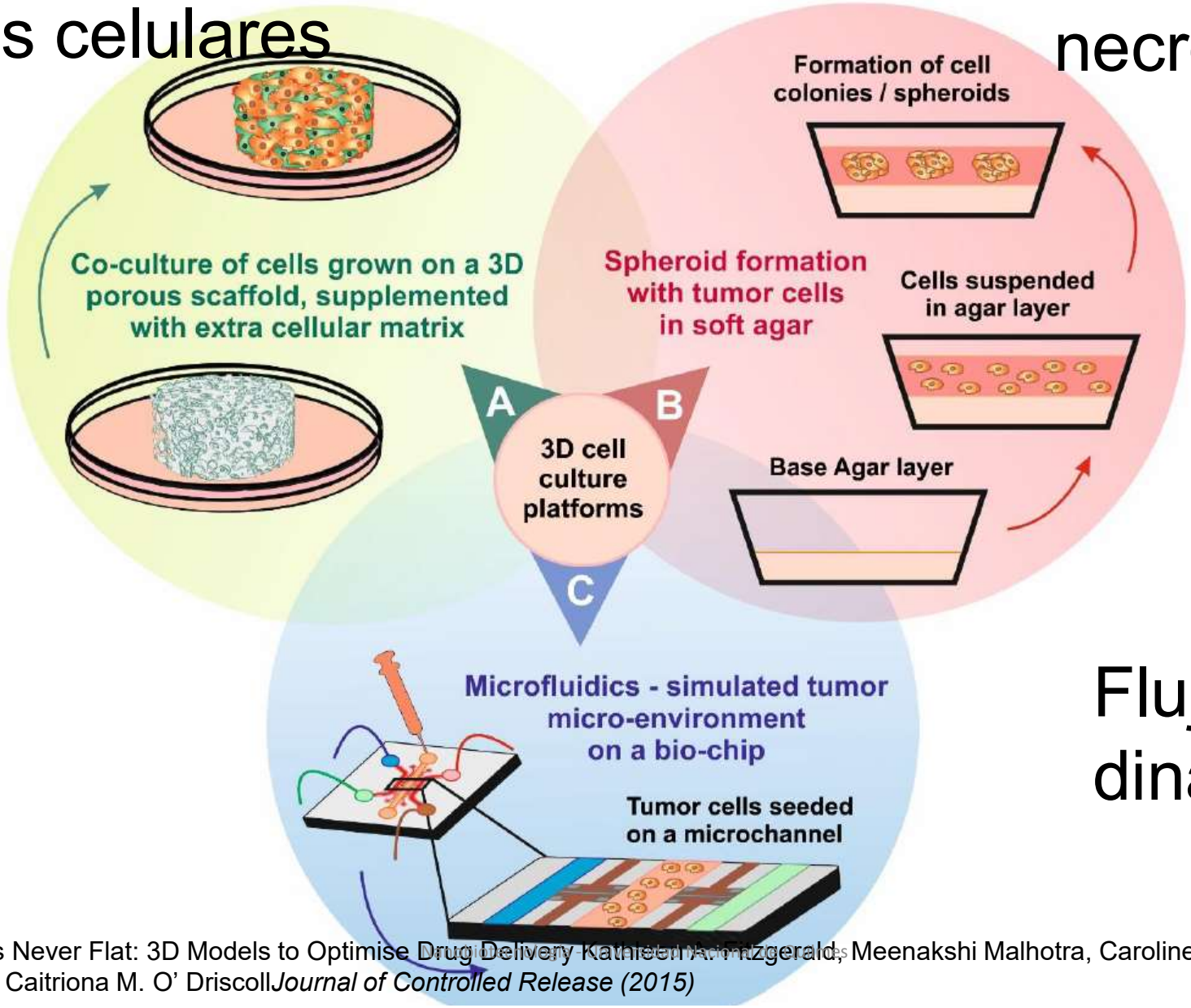
a mere **10% improvement in preclinical screening methods would reduce drug development costs by 100 million dollars per drug approved to the market** (I. Cavero, Optimizing the preclinical/clinical interface: an Informa Life Sciences conference 12-13 December, 2006, London, UK, Expert opinion on drug safety, 6 (2007) 217-224)

Life in 3D is Never Flat: 3D Models to Optimise Drug Delivery Kathleen A. Fitzgerald, Meenakshi Malhotra, Caroline M. Curtin, Fergal J. O' Brien, Caitriona M. O' Driscoll*Journal of Controlled Release (2015)*

Metodos de cultivos 3D en el labo

Diferentes tipos celulares

Interior necrotico



Flujo dinamico

Life in 3D is Never Flat: 3D Models to Optimise Drug Delivery Kathleen A. Fitzgerald, Meenakshi Malhotra, Caroline M. Curtin, Fergal J. O' Brien, Caitriona M. O' Driscoll*Journal of Controlled Release (2015)*

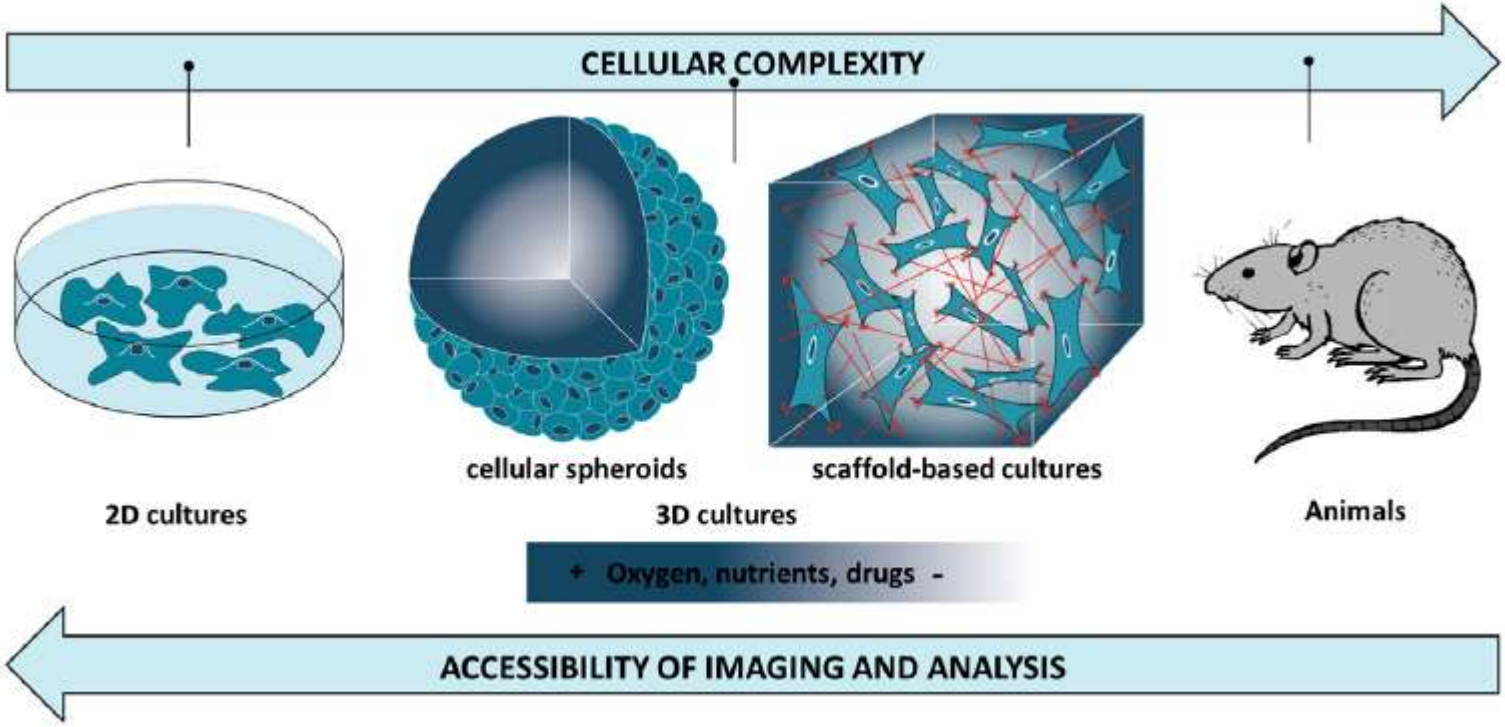
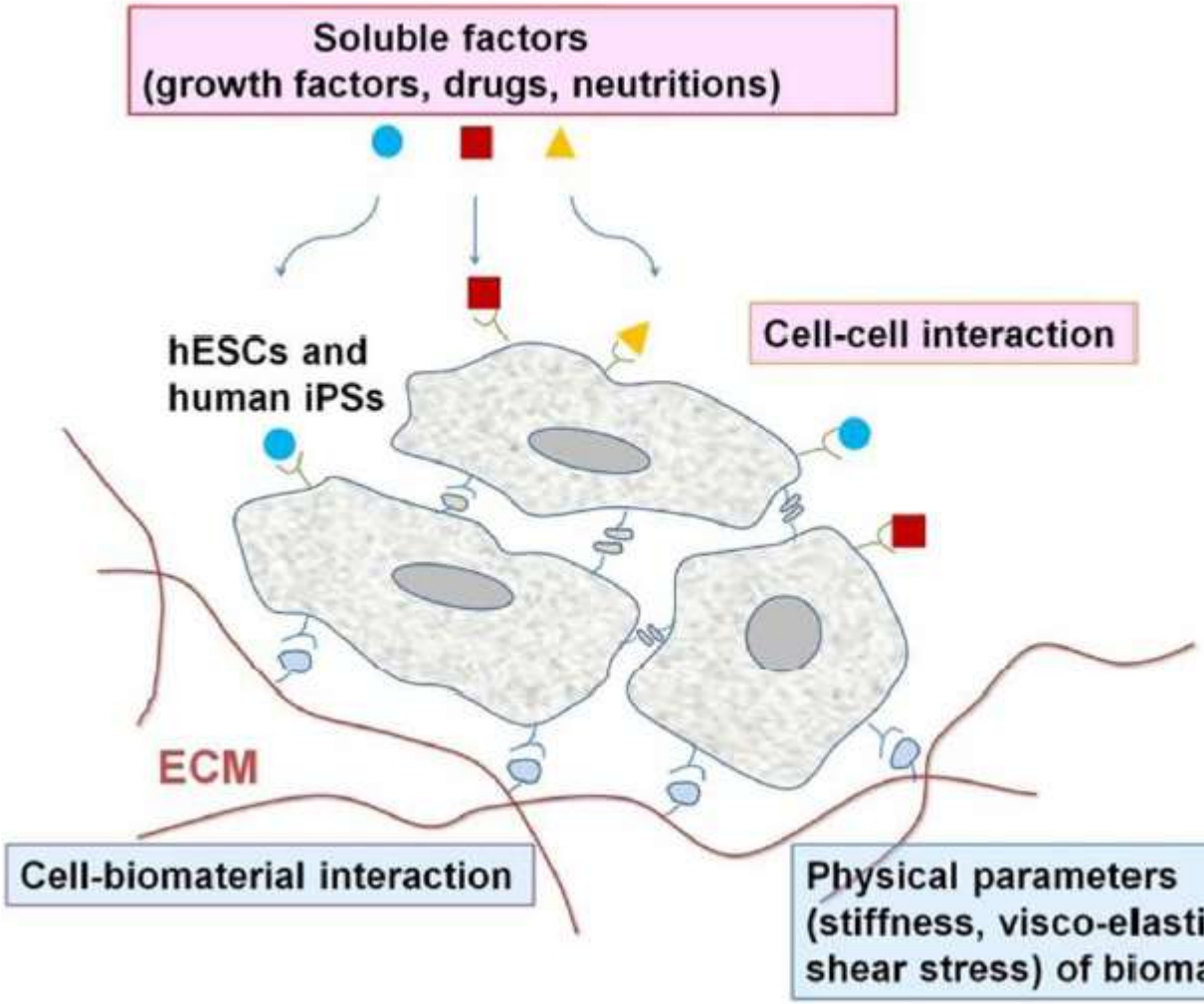


Fig. 4. Rethinking drug screening processes. Tissue engineering provides 3D cultures that recreate the complex cellular microenvironmentmore precisely than traditional 2D cultures, due to the incorporation ofmultiple physical,mechanical and chemical cues that arise fromECM–cell and cell–cell interactions. At the opposite end of the experimental continuum, animals do not capture important facets of human behavior and they are not feasible for HTS applications. Therefore, 3D cultures can bridge the gap between 2D cultures and animal models.

Las células son sensibles a su microentorno!



Several factors in the microenvironments of stem cells influence their fate:

(1)soluble factors

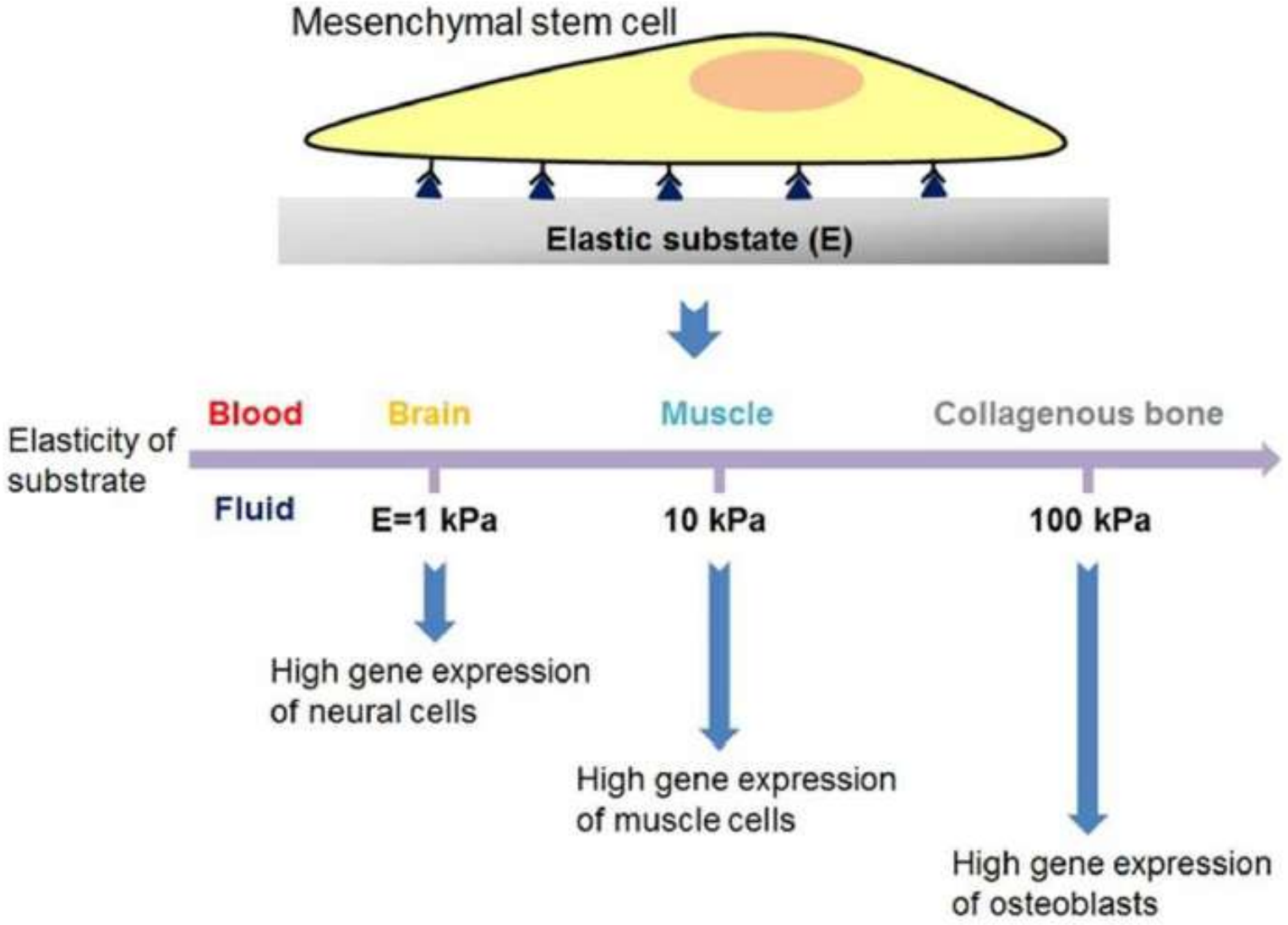
(2)cell-cell interactions

(3)cell biomacromolecule (or biomaterial) interactions

(4)physical factors, such as (a) the **concentration of oxygen** (e.g., **hypoxia condition**) (b) the **elasticity (rigidity)** of cell culture matrices (**biomaterials**), (c) the **topographies of cell culture biomaterials,** and (d) **the mechanical forces produced by cell culture biomaterials**

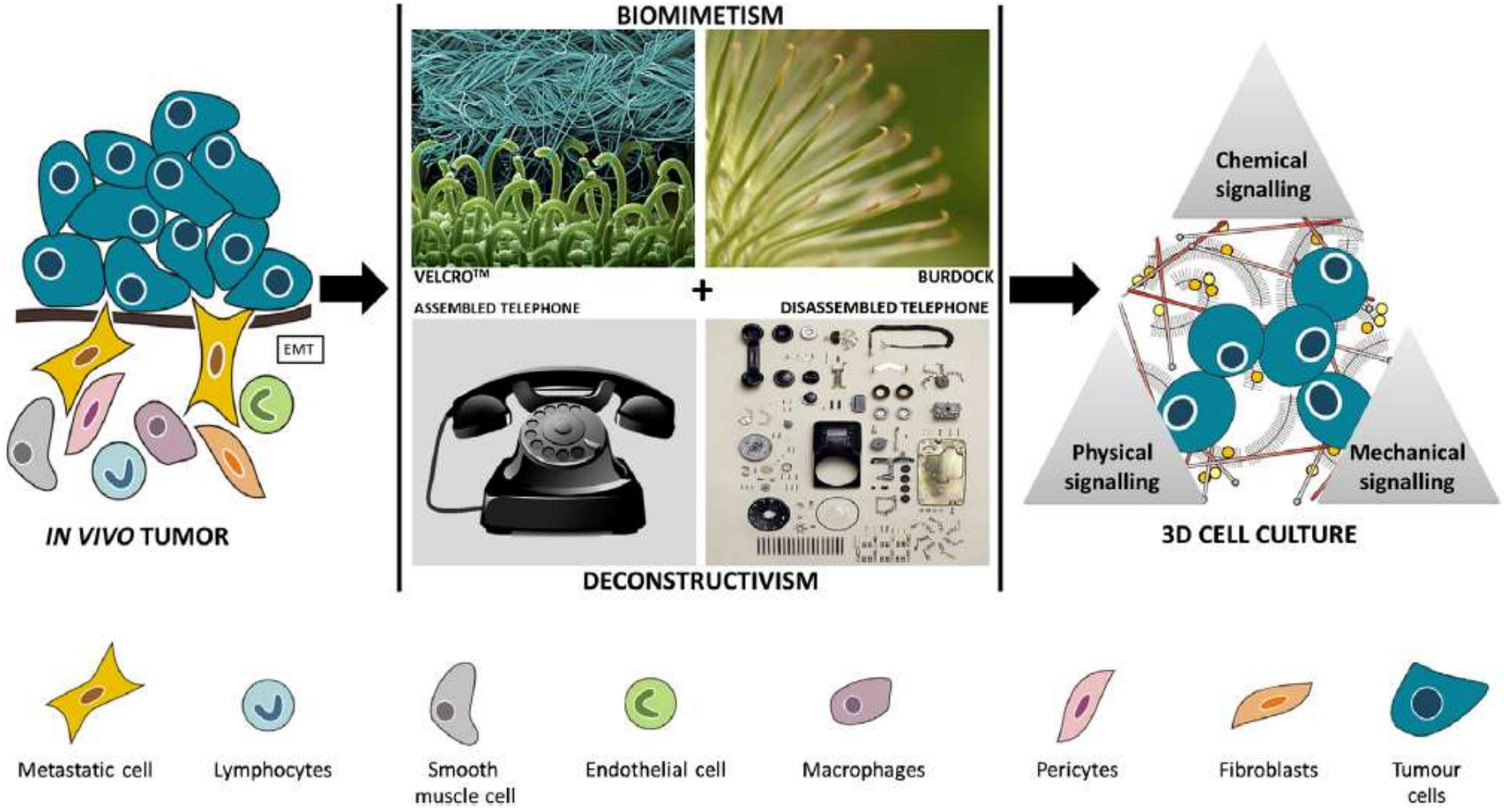
Cicada-inspired cell-instructive nanopatterned arrays Ting Diu1,2, Nilofar Faruqui1 , Terje Sjo¨stro¨m2 , Baptiste Lamarre1 , Howard F. Jenkinson2 , Bo Su2 & Maxim G. Ryadnov1,3: Diu, T.et al. Cicada-inspired cell-instructive nanopatterned arrays. Sci. Rep. 4, 7122; (2014).

La elasticidad de MEC (prop. física) determina la expresión genética de células en cultivo!!



A. Higuchi, Q. Ling, S. S. Kumar, Y. Chang, A. A. Alarfaj, M. A. Munusamy, K. Murugan, S. Hsu and A. Umezawa, **Physical cues of cell culture materials lead the direction of differentiation lineages of pluripotent stem cells** *J. Mater. Chem. B, 2015,*

Bioingenieria: Principios de diseño 3D: Biomimetismo (ideas de la naturaleza) + deconstructivismo (simpler more predictable)

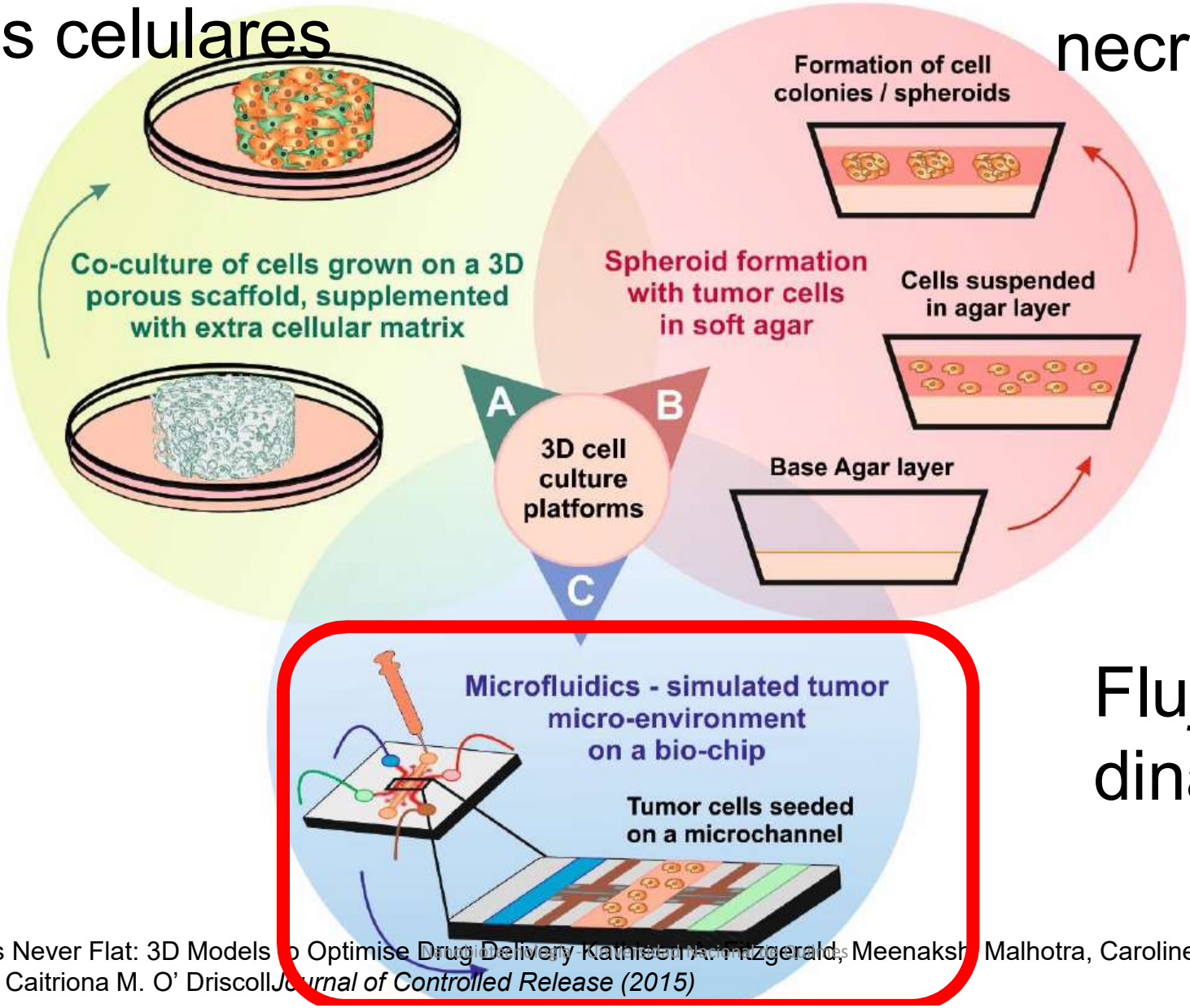


Bioengineering 3D environments for cancer models. Mireia Alemany-Ribes, Carlos E. SeminoAdvanced Drug Delivery Reviews xxx (2014) xxx–xxx

Metodos de cultivos 3D en el labo

Diferentes tipos celulares

Interior necrotico



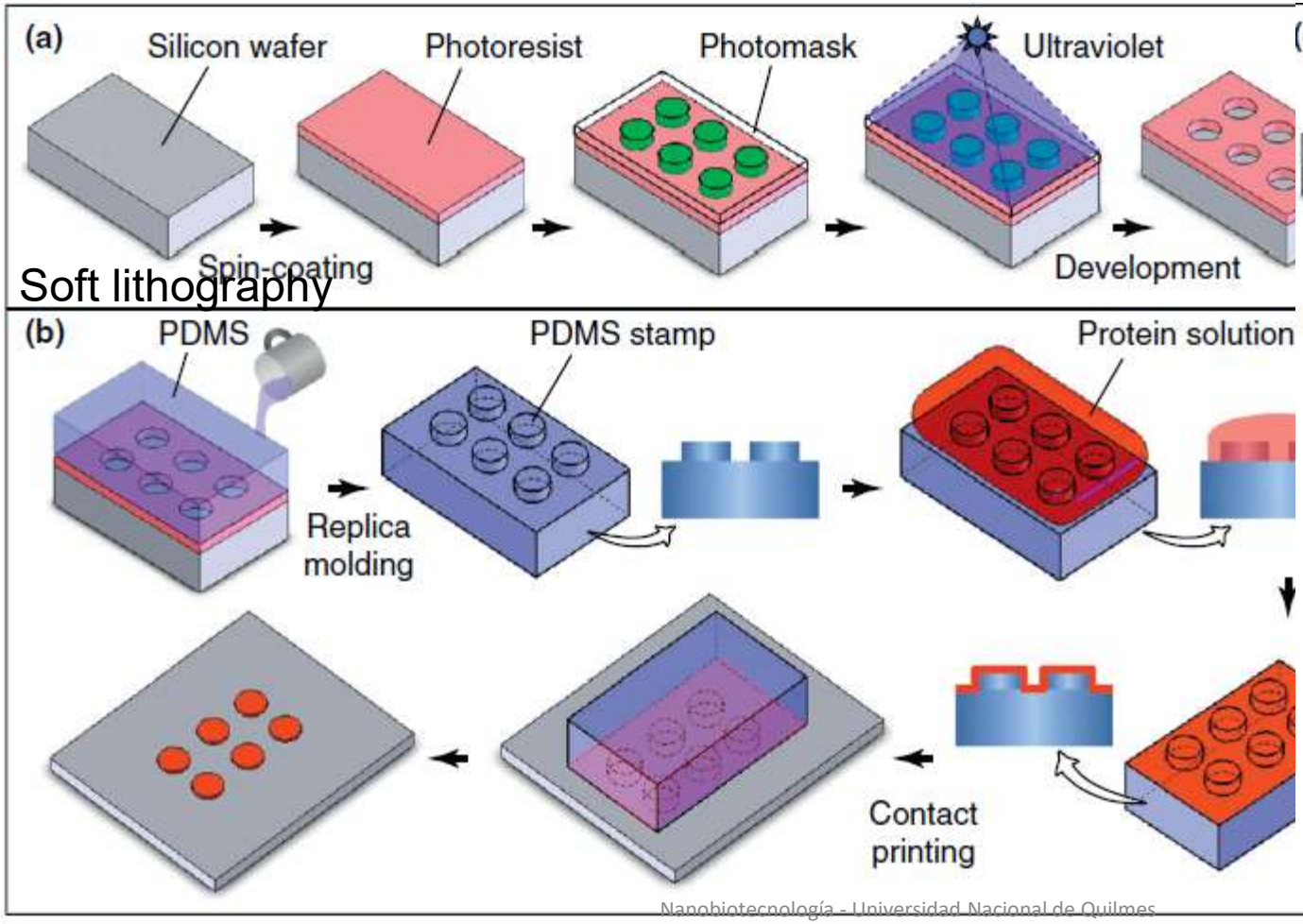
Flujo dinamico

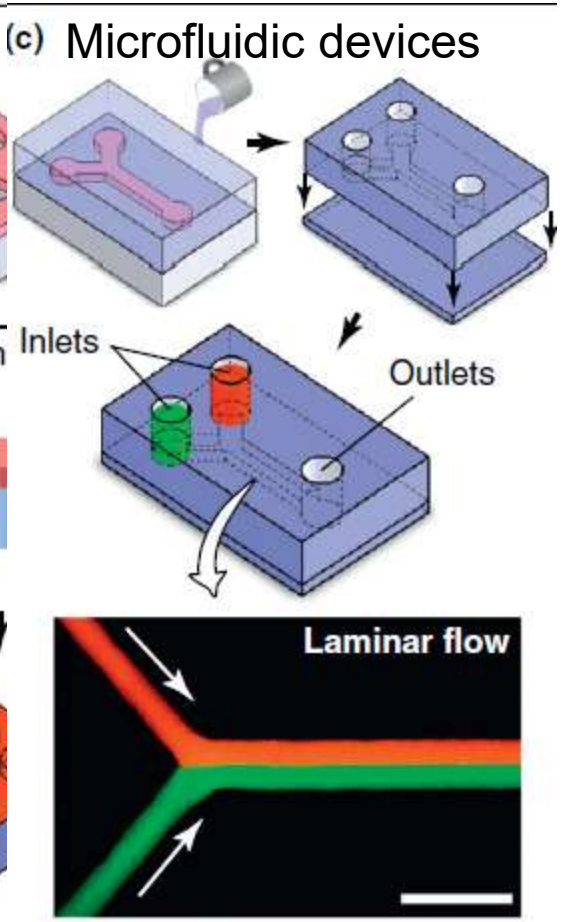
Life in 3D is Never Flat: 3D Models to Optimise Drug Delivery Kathleen A. Fitzgerald, Meenaksh Malhotra, Caroline M. Curtin, Fergal J. O' Brien, Caitriona M. O' Driscoll*Journal of Controlled Release (2015)*

Microengineering technologies used to construct 3D culture systems and organs-on-chips

Photolithography

silicone rubber poly(dimethylsiloxane) (PDMS)





Es posible controlar el crecimiento celular en la microescala

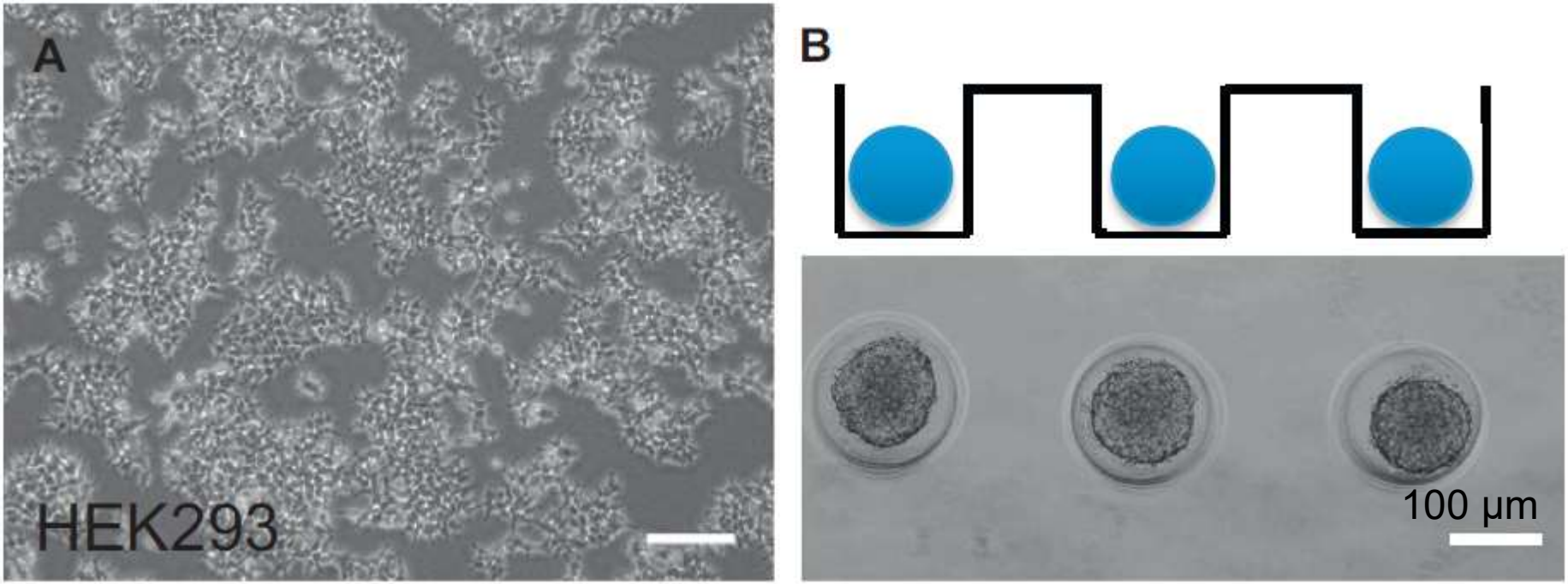
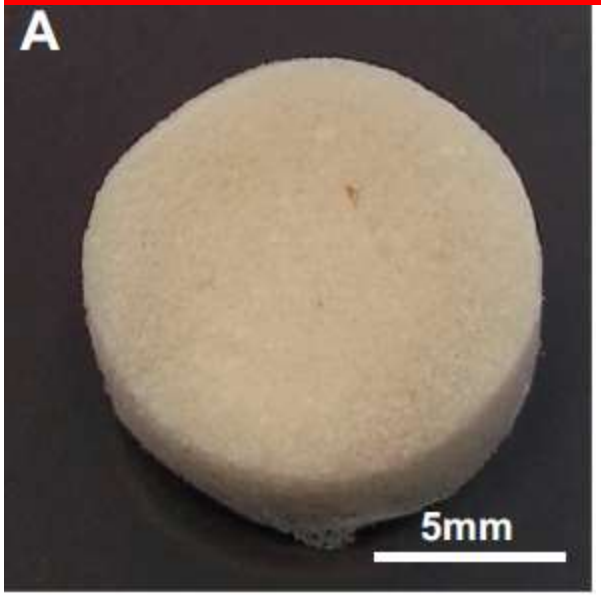
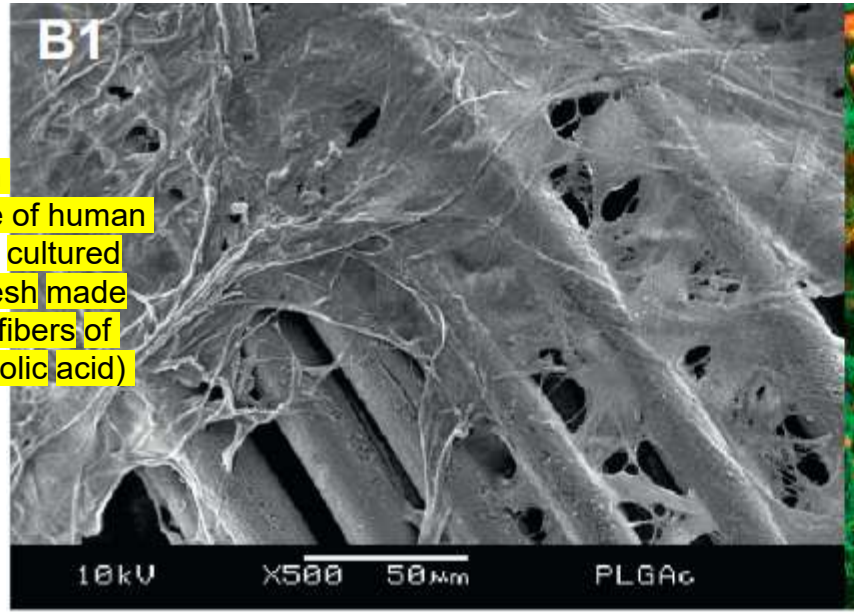


Fig. 2. Examples of cell spheroids as the simplest andmost convenientmodel of 3D cell culture. A) Human embryonic kidney cells (HEK293) in 2D culture. B) HEK293 cells in suspensions added to non-adherent agarose molds of defined size to encourage cell–cell adhesion, resulting in spheroids of sizes defined by them old diameter.

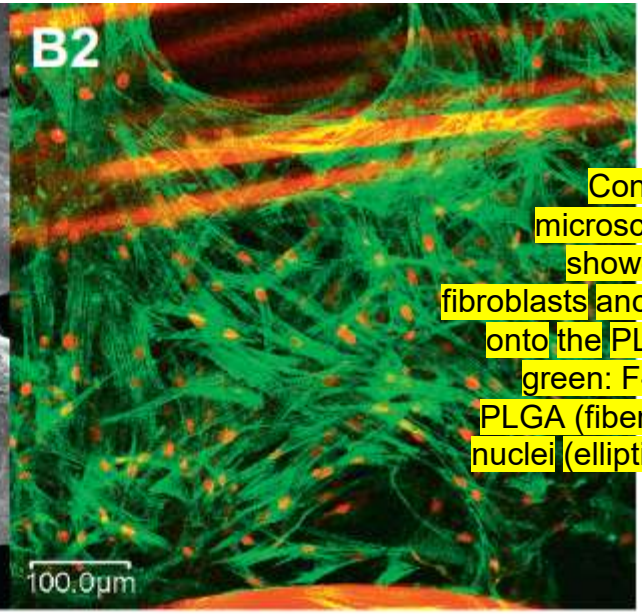
Matrices 3D mas comunes



A) A microporous sponge made from human hair keratins.



Scanning electron microscopy image of human dermal fibroblasts cultured on a 3D textile mesh made by knitting 20 µm fibers of poly(lactic-co-glycolic acid) (PLGA; 90:10).



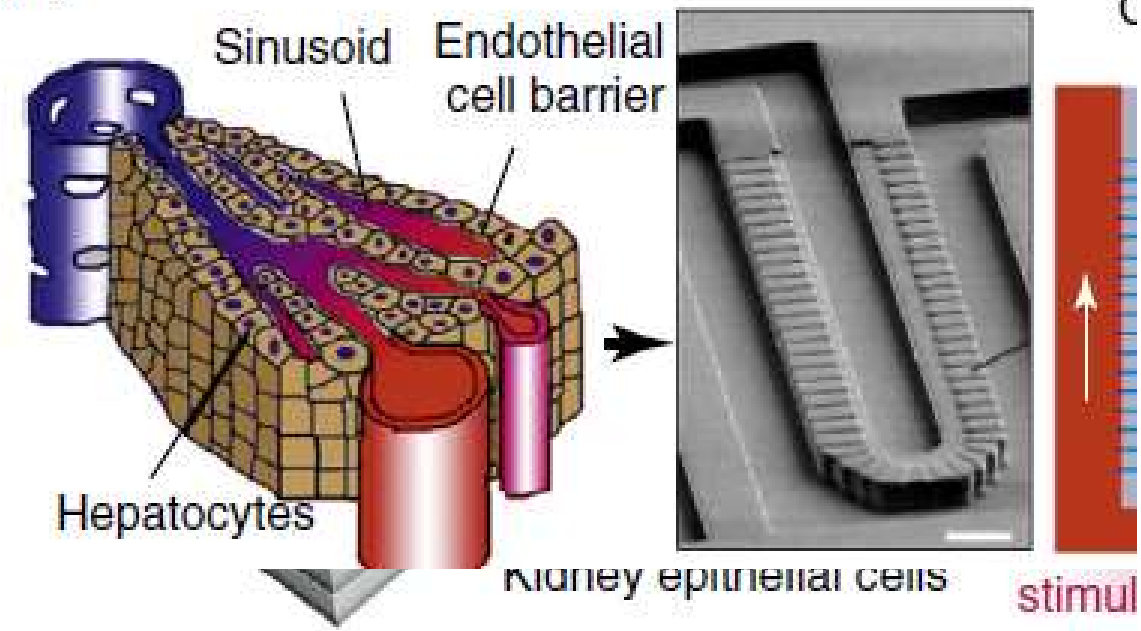
Confocal laser microscopy image showed that the fibroblasts anchored well onto the PLGA fibers. green: F-actin; red: PLGA (fibers) and cell nuclei (elliptical spots).

Advanced Drug Delivery Reviews xxx (2014) xxx–xxx Probing the relevance of 3D cancer models in nanomedicine research☆
David T. Leong a,⁎,1, KeeWoei Ngb

Organos-on-chips: miniaturizacion, inte control multiparametros: gradientes stress, cell patterning, interfase teji organo-organo : imitando microentono organos human

(a) **Riñón en un chip**

(b) **Hígado en un chip**



Interaccion heterotipica

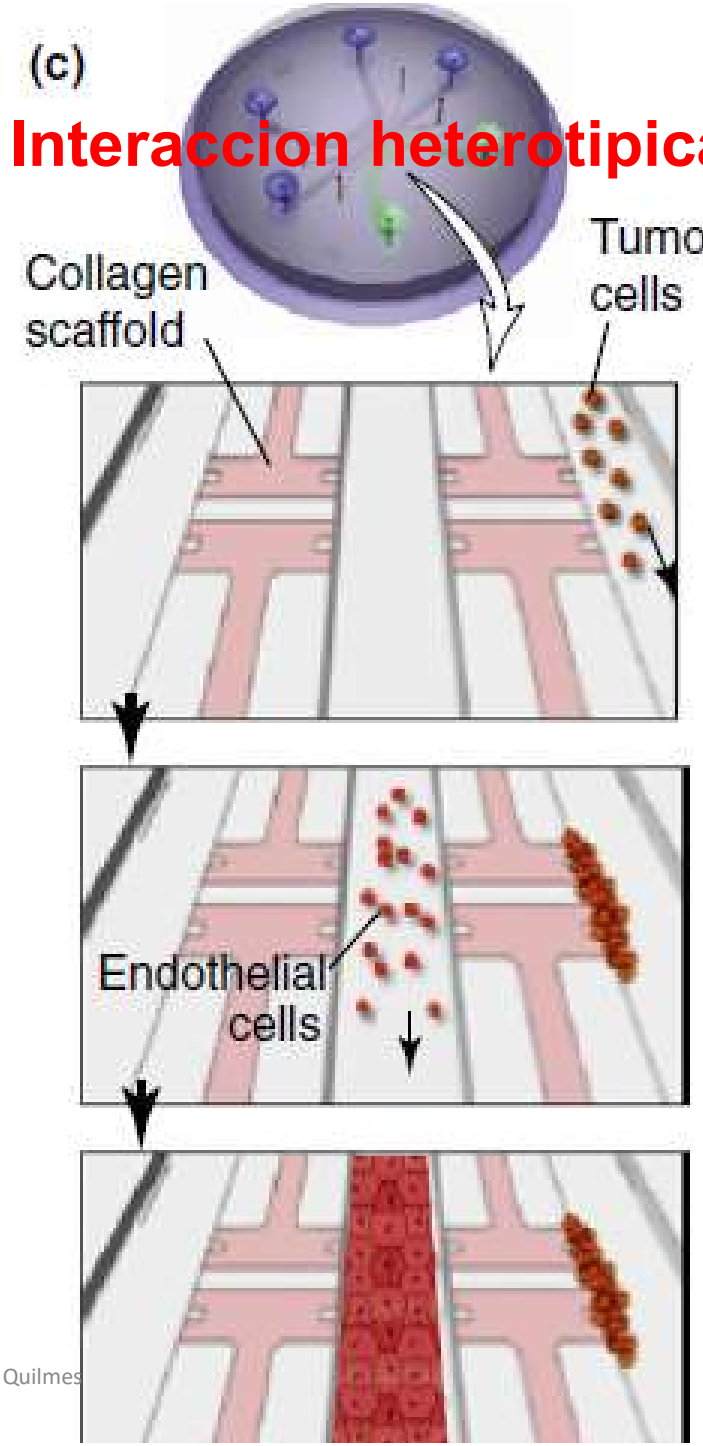
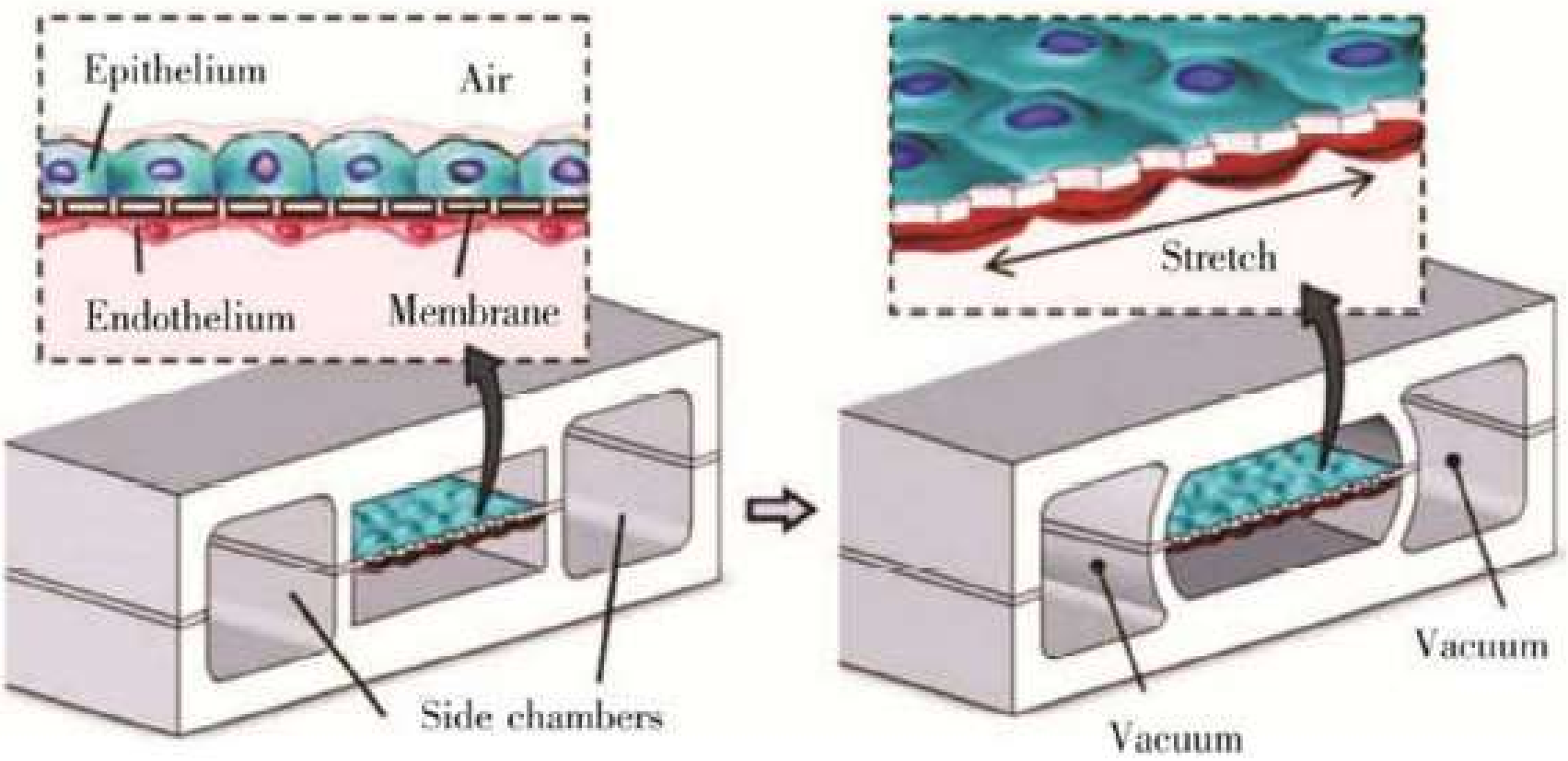


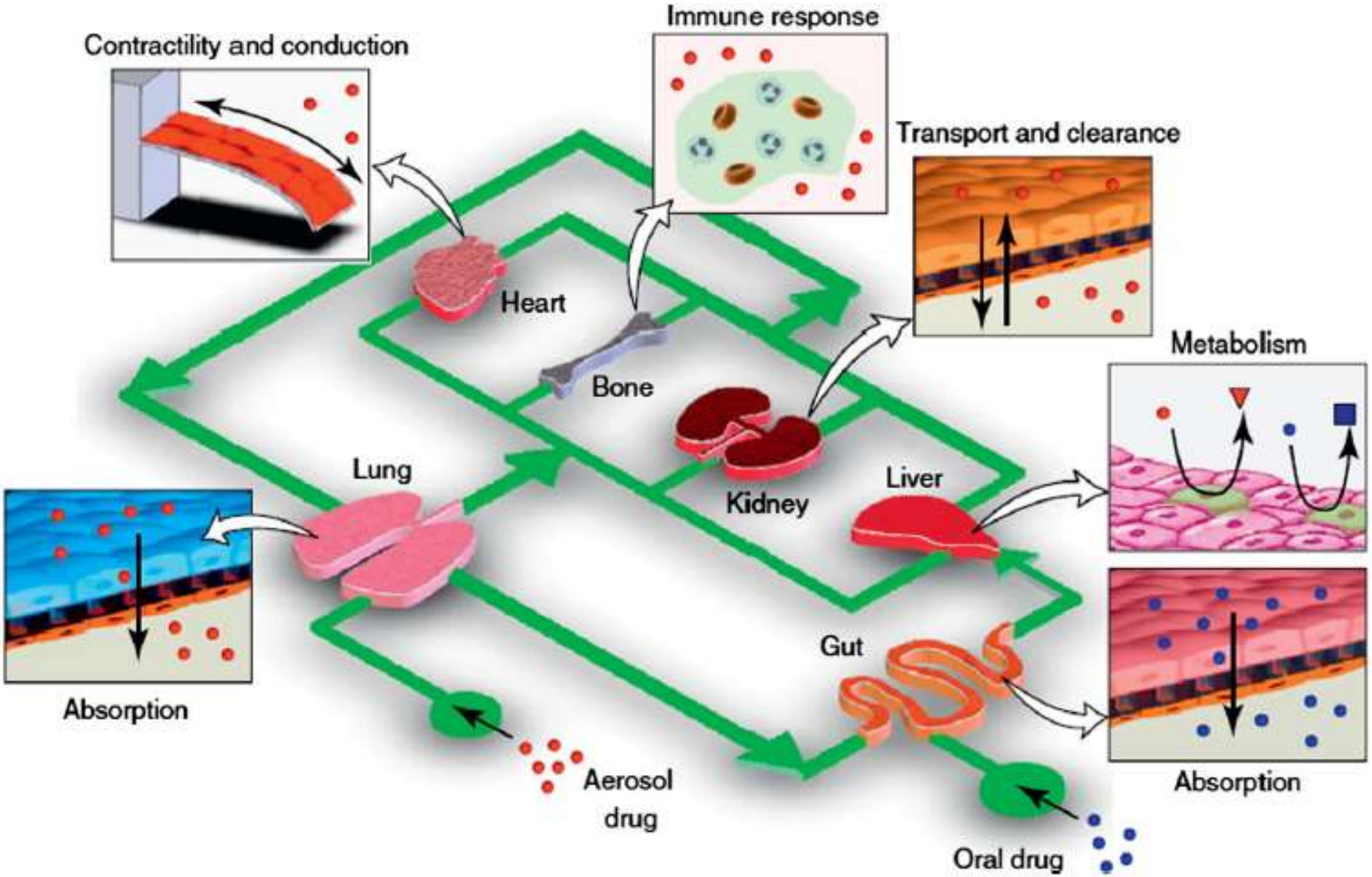
Figure 2. Microengineered organs-on-chips. (a) A microfluidic kidney epithelium i incorporates stacked layers of PDMS microchannels and a PDMS well separate architecture of this microsystem provides physiologically relevant culture environ

Pulmon en un chip



Organs-on-chips and Its Applications. SUN Wei1, CHEN Yu-Qing, LUO Guo-An, ZHANG Min, ZHANG Hong-Yang, WANG Yue-Rong,HU Ping. CHINESE JOURNAL OF ANALYTICAL CHEMISTRY Volume 44, Issue 4, April 2016

The human-on-a-chip concept: sistema integrado



Trends Cell Biology, 21, Huh, D.; Hamilton, G.A.; Ingber, D.E., From 3D cell culture to organs-on-chips, Pages No. 745–754, © (2011), with permission from Elsevier. 4 E.L. da Rocha et al. / Materials Science and Engineering C xxx (2013) xxx–xxx

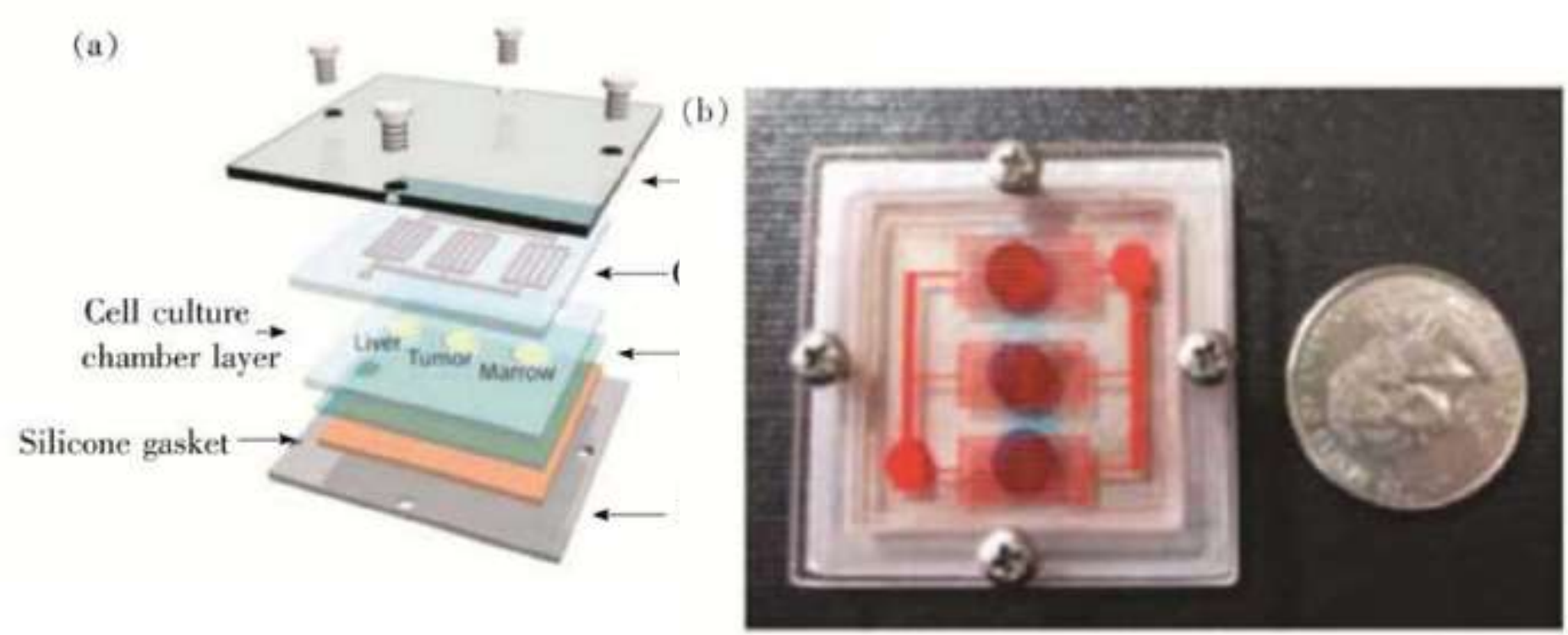
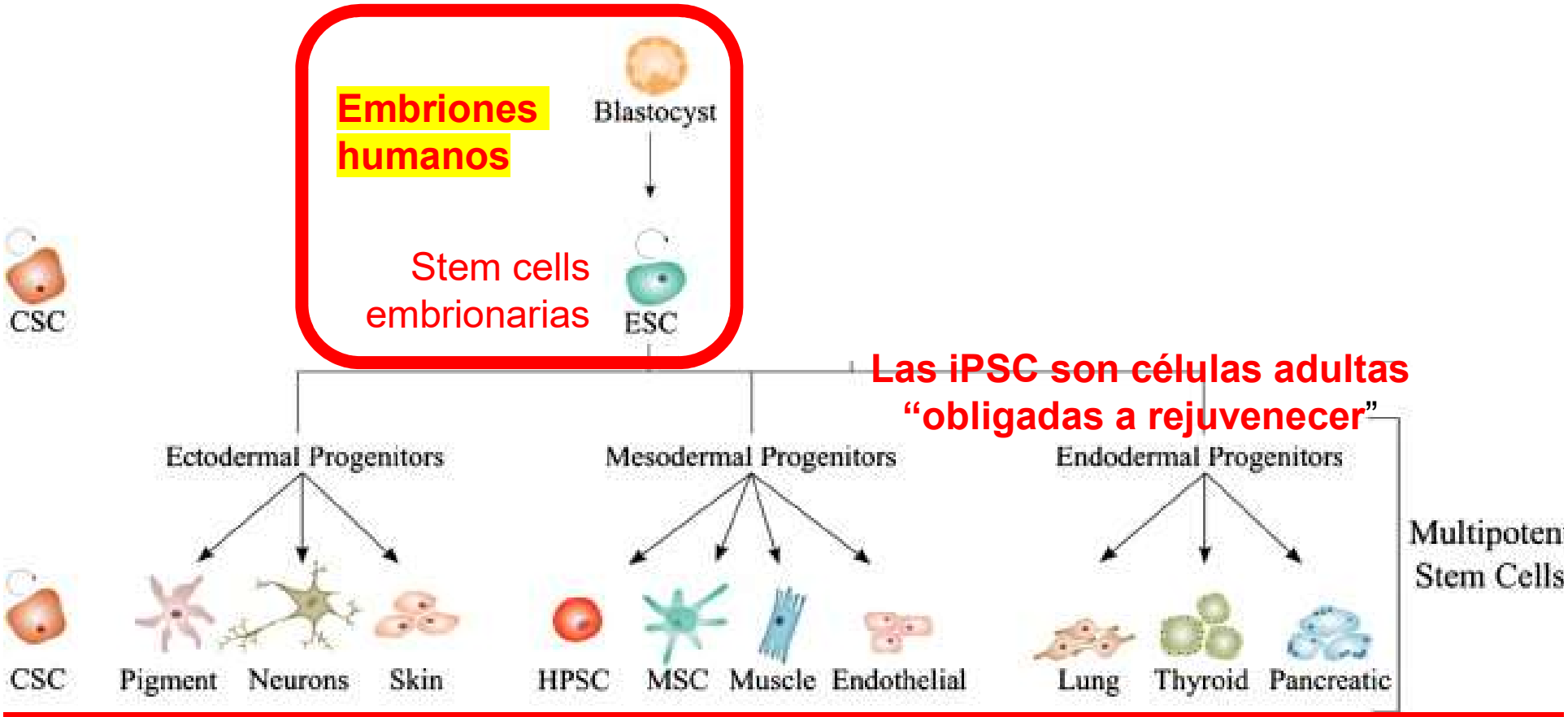


Fig.3 A multi-organ microfluidic framework[59]
a. Schematic of layered multi-organ chip; b. Picture of the assembled device

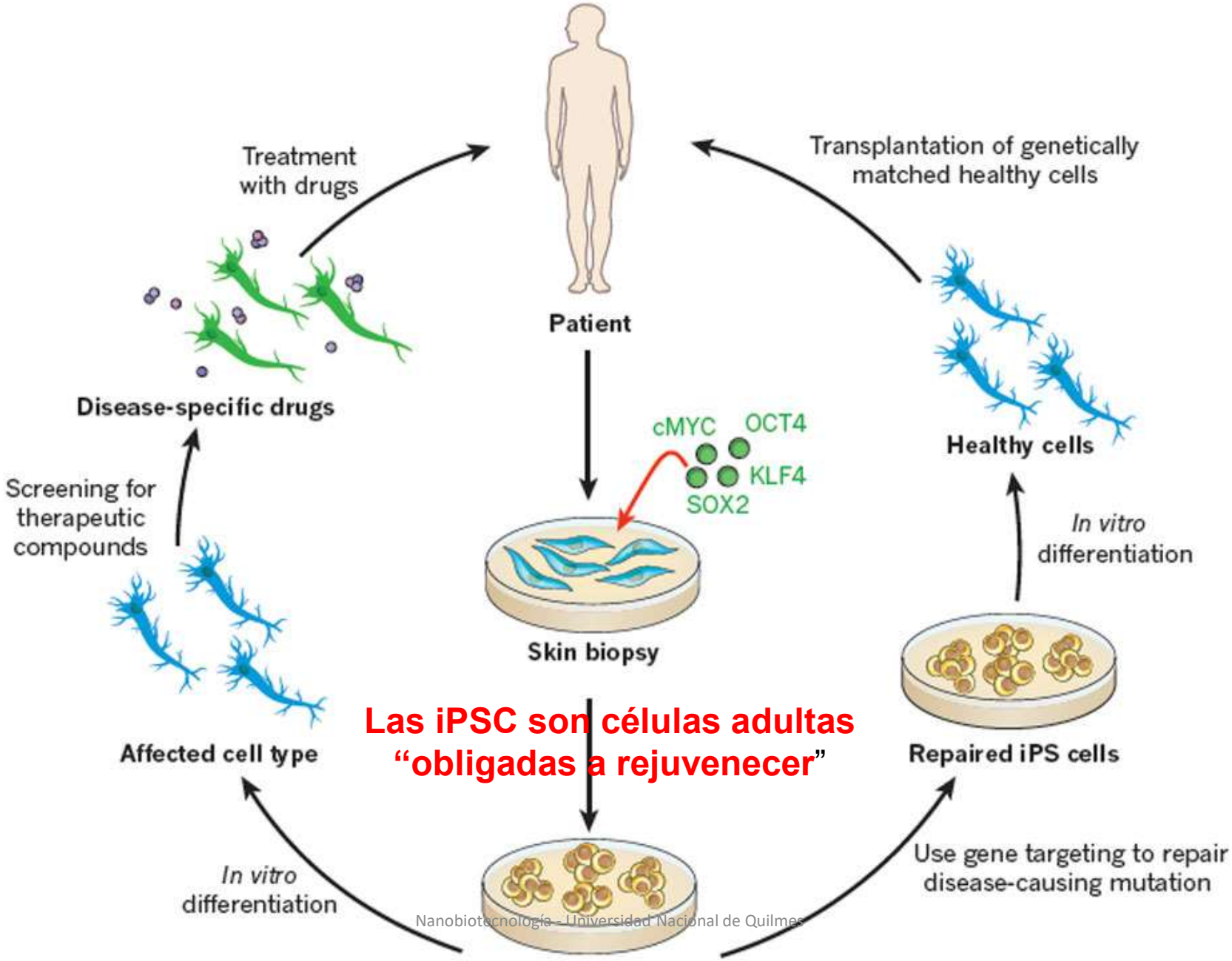
Organs-on-chips and Its Applications. SUN Wei1, CHEN Yu-Qing, LUO Guo-An, ZHANG Min, ZHANG Hong-Yang, WANG Yue-Rong,HU Ping. CHINESE JOURNAL OF ANALYTICAL CHEMISTRY Volume 44, Issue 4, April 2016

Ingenieria de tejidos/regeneración de organos
Problema ético: origen de las *stem cells*

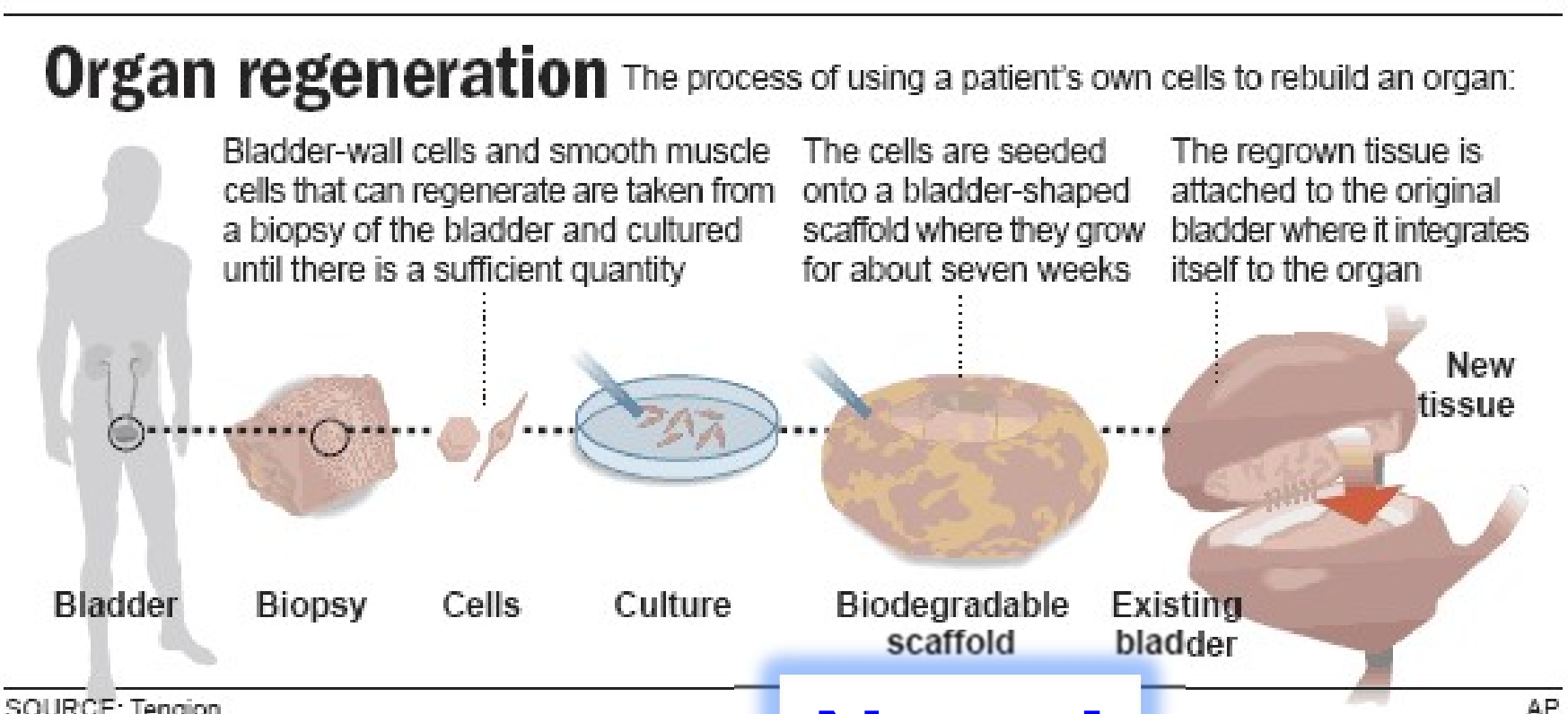


Ingenieria de tejidos/regeneración de organos
Reprogramación celular: **volviendo atrás el reloj**

Reprogramación celular: **volviendo atrás el reloj**

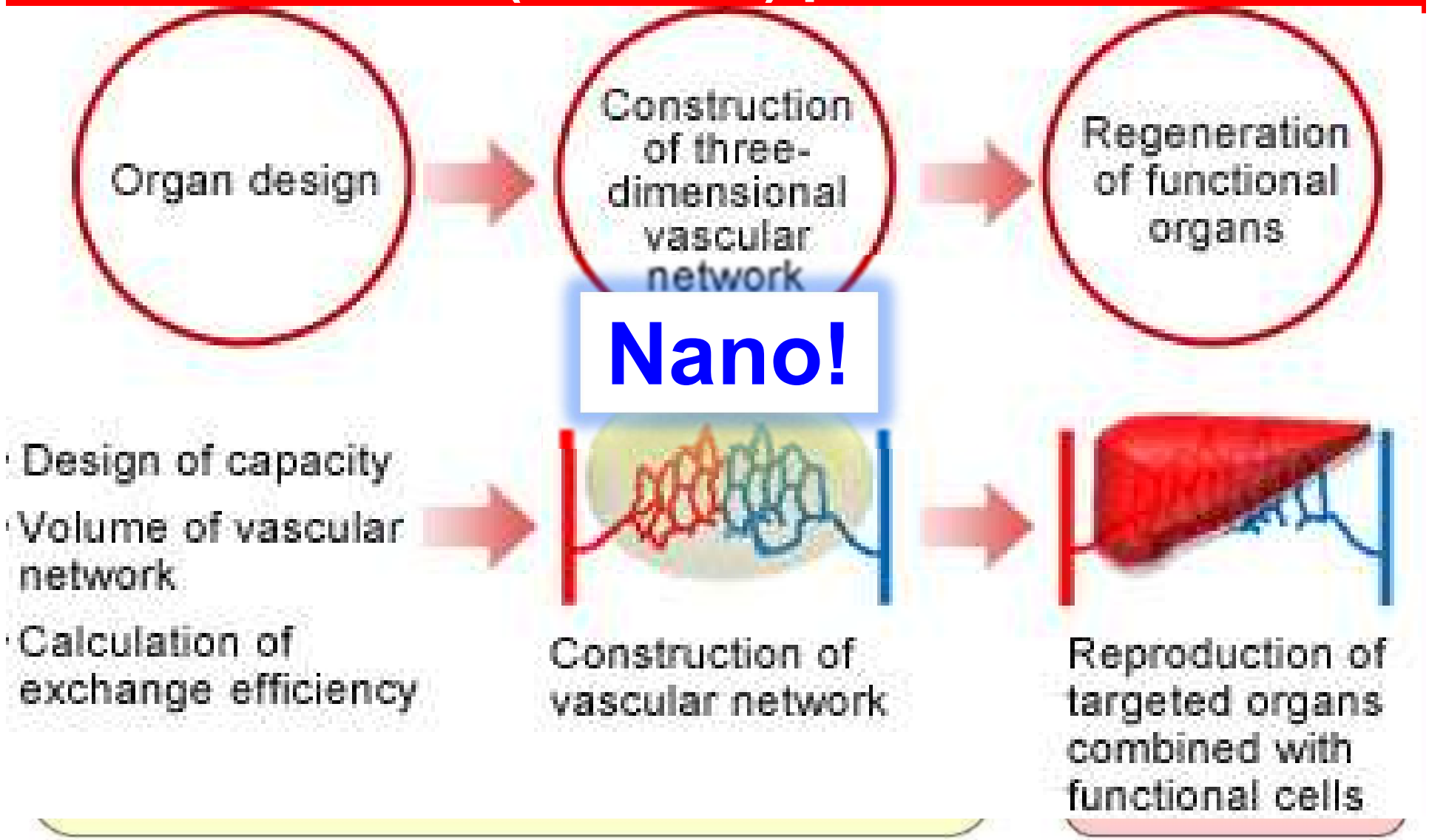


Regeneracion de órganos: necesidad de un "armazón" (*scaffold*) para las celulas



Nano!

Regeneracion de órganos: necesidad de un "armazón" (*scaffold*) para las celulas



2. Regenerative Medicine and 3D Printing

Organ Regeneration

Nano!

Whole Organ Decellularization and Recellularization (Heart)

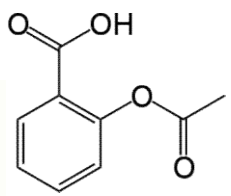
Personalized 3D Models

Lab-grown Meat

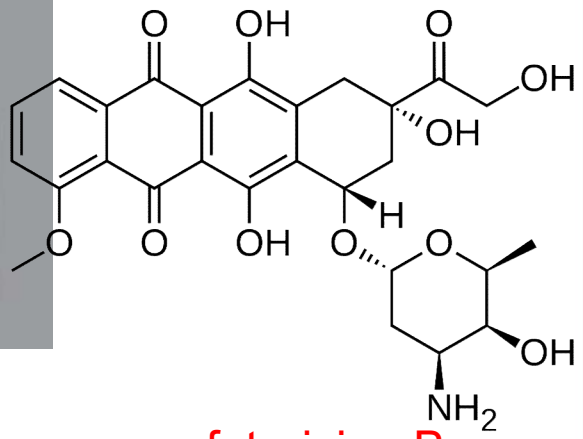
Nanobiotecnologia: un nuevo paradigma en terapéutica

Terapéutica basada en pequeñas moléculas

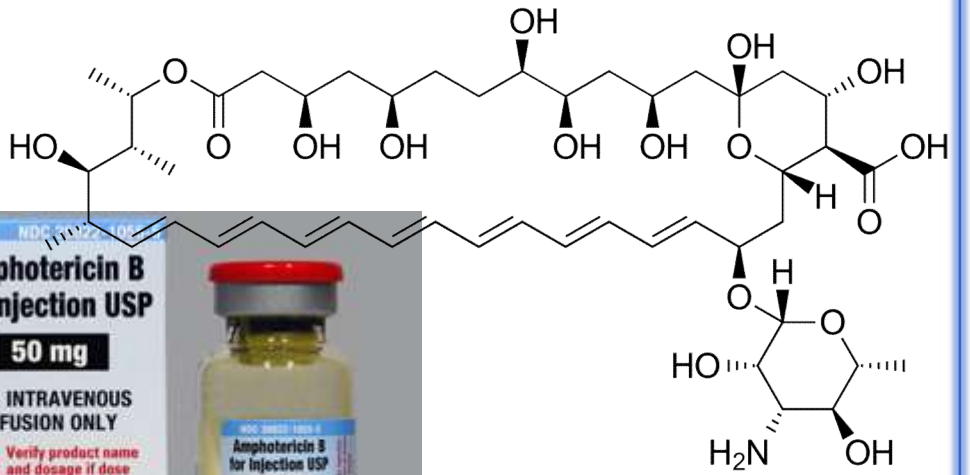
acido acetil salicílico



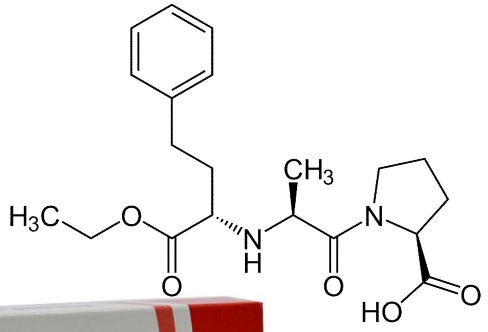
doxorubicina



anfotericina B



enalapril



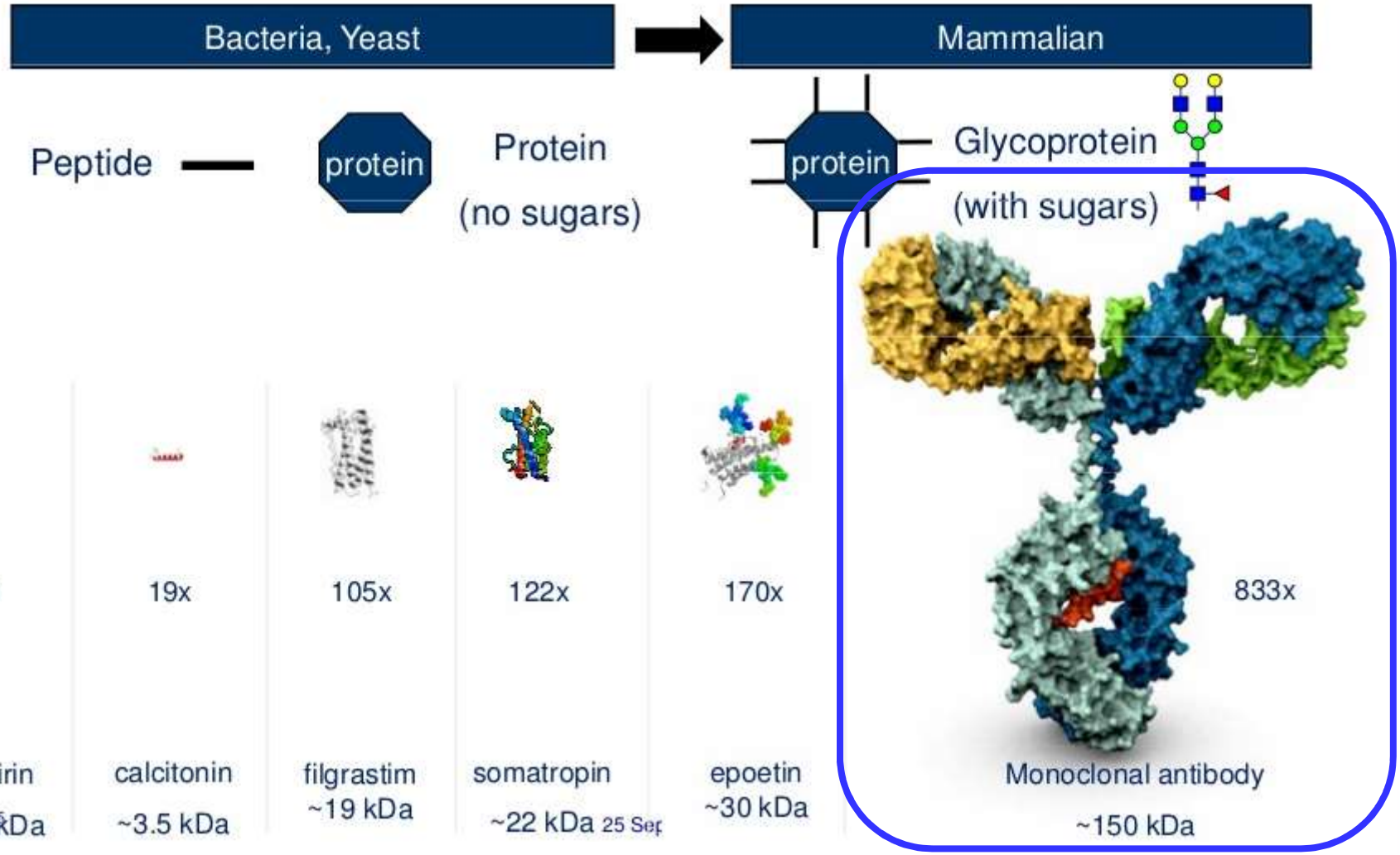
Terapéutica basada en pequeñas moléculas

Terapéutica basada en pequeñas moléculas

Ausencia de selectividad: efectos colaterales pueden ser mortales

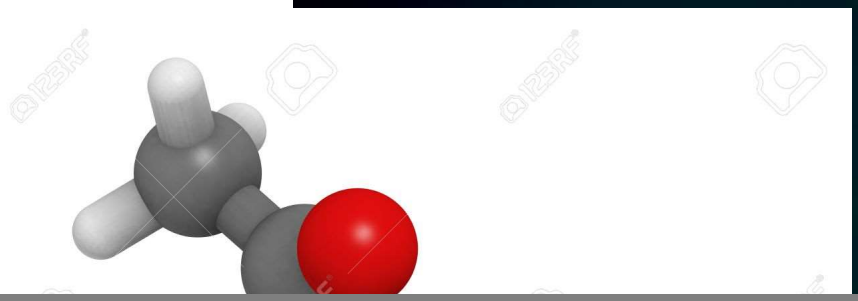
Terapéutica basada en productos biológicos

Mayor complejidad estructural. **selectividad**

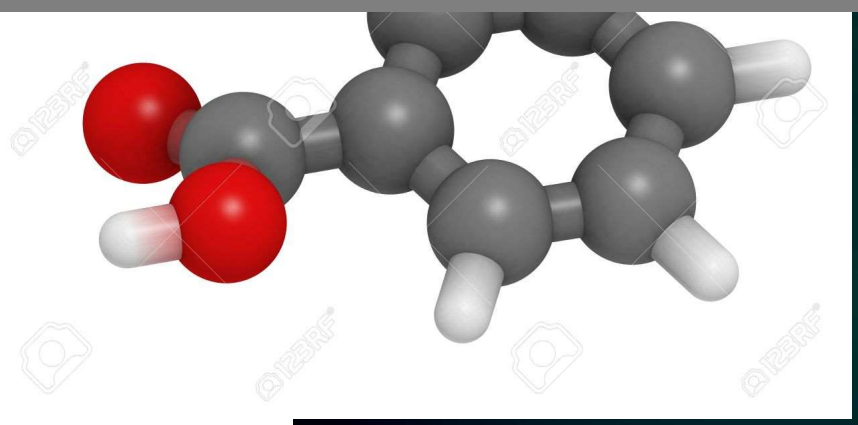


Tomado de IFPMA

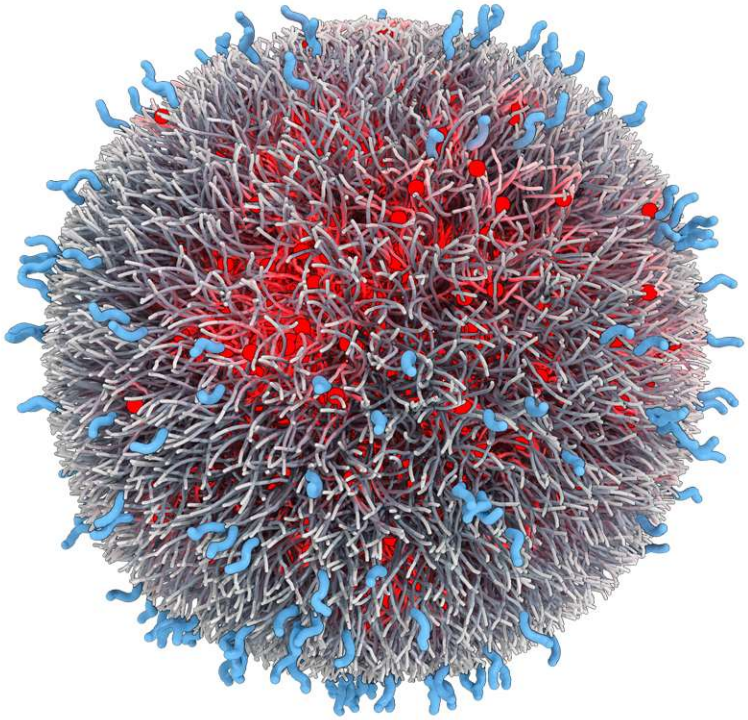
Terapéutica basada en pequeñas moléculas o en productos biológicos: ¿que tienen en común?



Su PK/BD/TI/**actividad** depende de estructura primaria-secundaria-terciaria

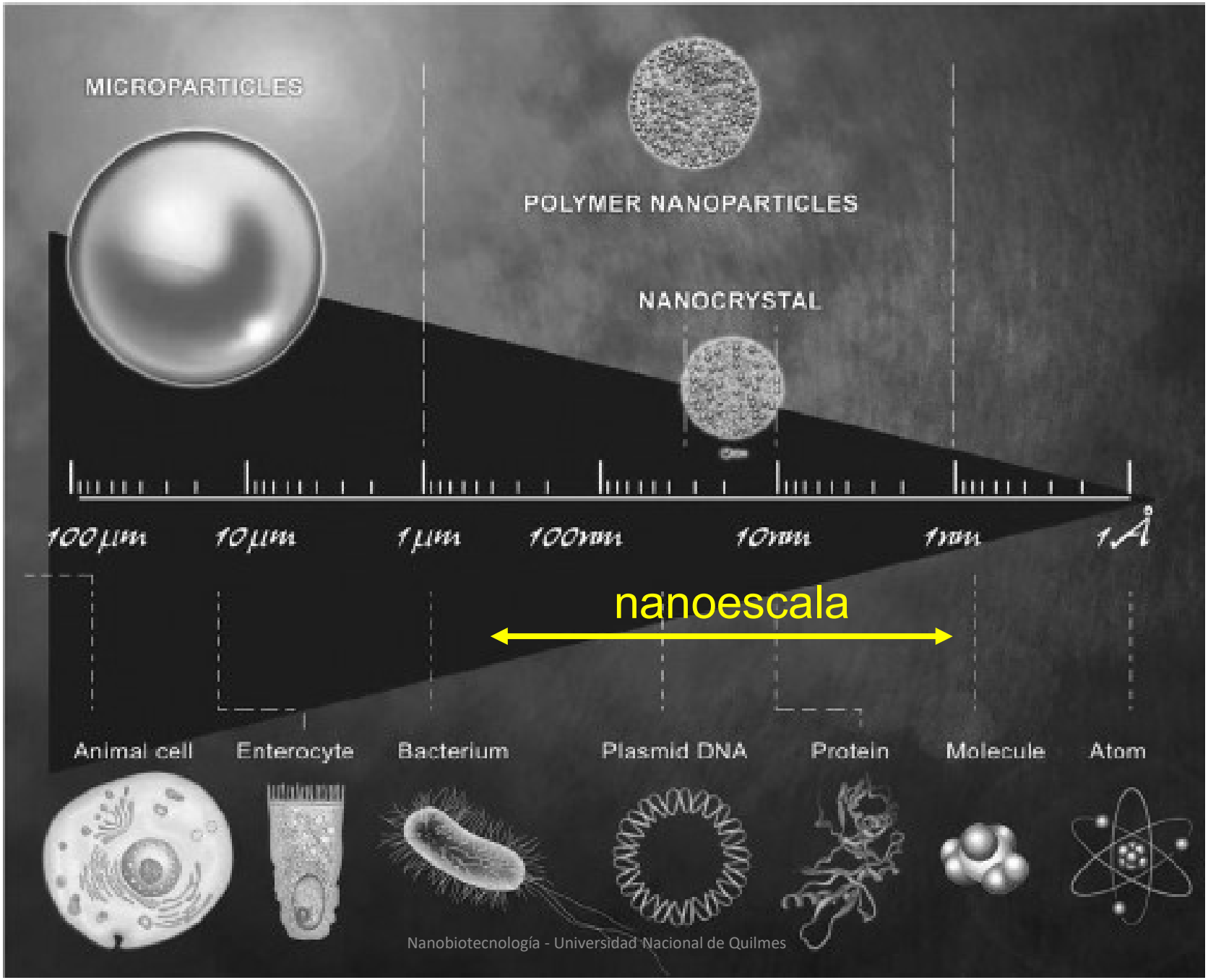


Nanomedicinas: un nuevo paradigma terapéutico



\+ API (ingrediente farmacéuticamente activo) = nanomedicina

Nanomedicinas: farmacocinética, biodistribucion y trafico intracelular [actividad terapéutica] independientes de estructura del API y dependientes de estructura del nano-objeto


MICROPARTICLES
POLYMER NANOPARTICLES
NANOCRYSTAL
100 µm
10 µm
1 µm
100 nm
10 nm
1 nm
1 Å
nanoescala
Animal cell
Enterocyte
Bacterium
Plasmid DNA
Protein
Molecule
Atom

Nanomedicinas: un nuevo paradigma terapéutico

tratamientos **menos tóxicos (selectivos)**, mas cortos, ¿mas eficaces?


CUANDO ALGO ES LINDO
NO NECESITA MARKETING.