The Era of Biosimilars and Nanosimilars
Current Perspectives

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PATENT LAW • NANOMEDICINE • BIODEFENSE

TEVA

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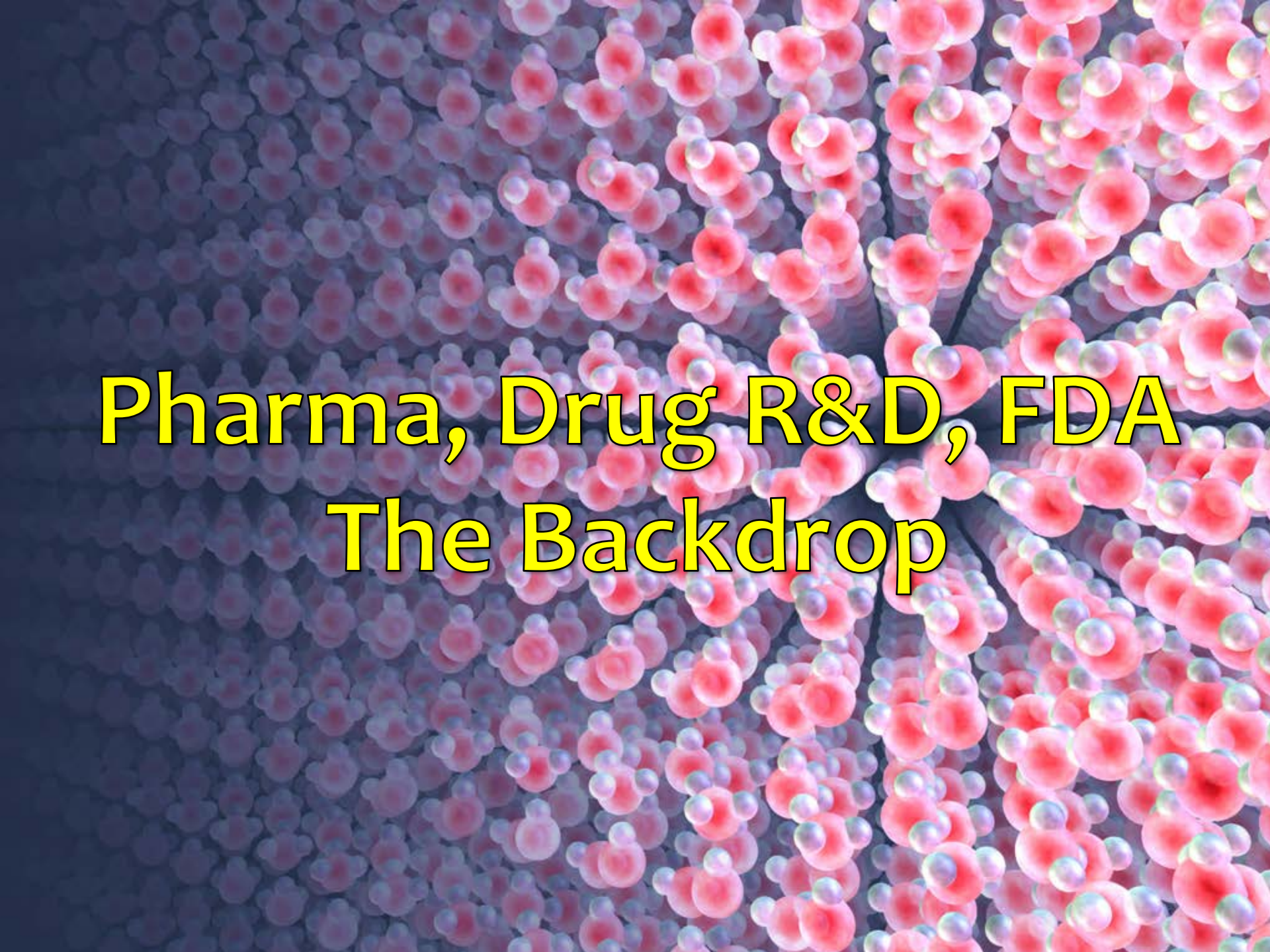
ACCELSIORS

Presentations and Papers

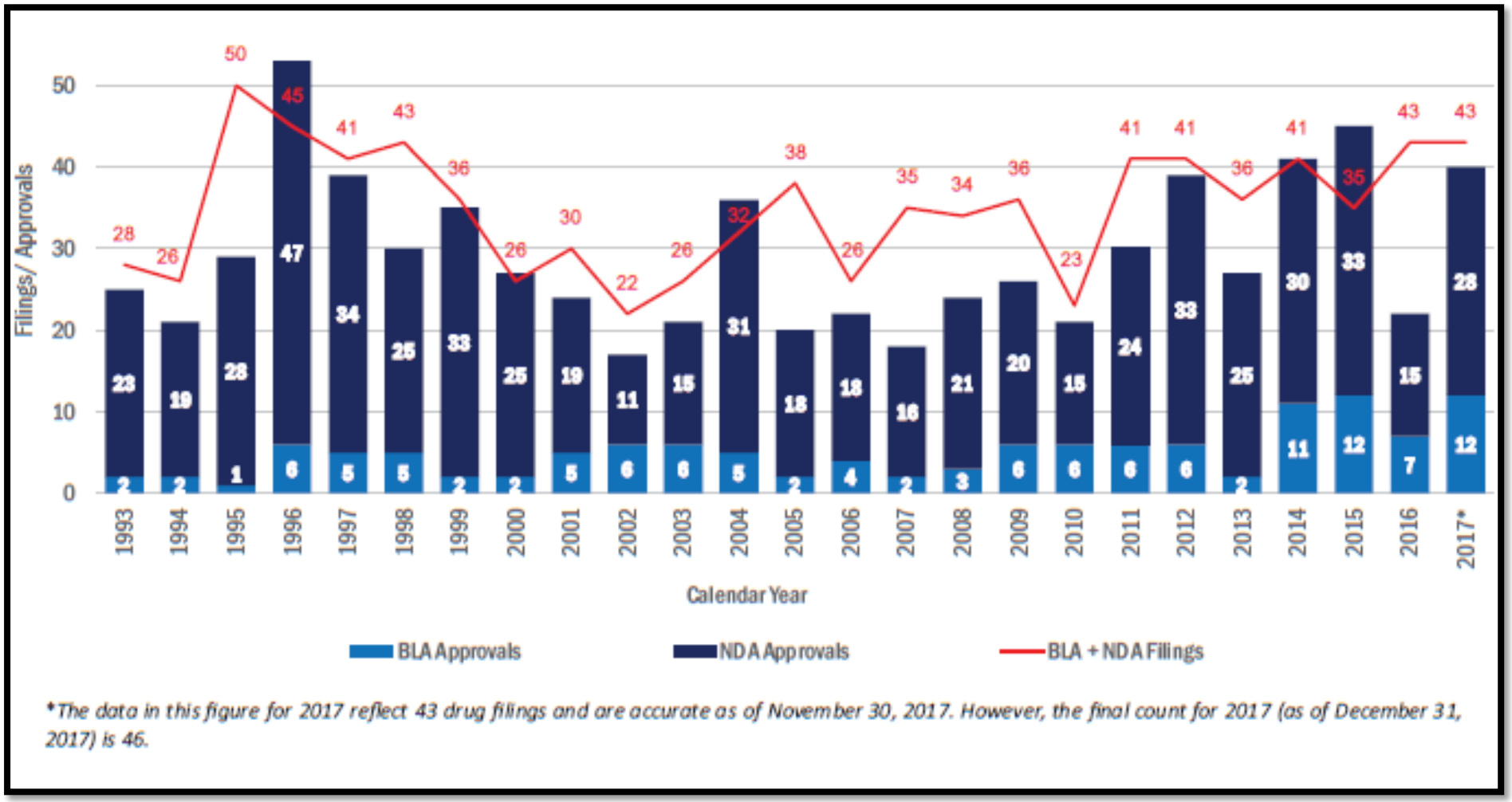
Free Downloads: https://www.nanomedus.org


Pharma, Drug R&D, FDA
The Backdrop

Converging technologies, emerging markets, and evolving regulations.

"I understand they're going to connect them. The Provost ordered it."

Downward Trend in New Drugs?



**The data in this figure for 2017 reflect 43 drug filings and are accurate as of November 30, 2017. However, the final count for 2017 (as of December 31, 2017) is 46.*

In many cases, developers have no choice but to use the tools and concepts of the last century to assess this century's candidates. -FDA

Drug Design and Development

Main Finding:

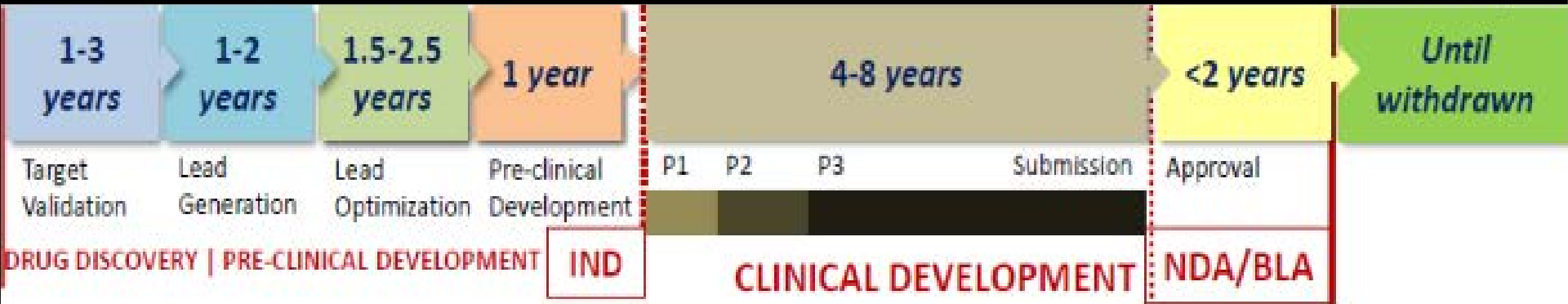
The estimated average pre-tax industry cost per new prescription drug approval (inclusive of failures and capital costs) is:

$2,558 million

Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

$2.6 billion in 2013 dollars, up 145% from the previous 2003 study

Pharma Timelines and Attrition



	Phase I to Phase II	Phase II to Phase III	Phase III to Submission	Submission to Approval
Small molecule	63%	38%	61%	91%
Large molecule	84%	53%	74%	96%

Clinical trial success rates

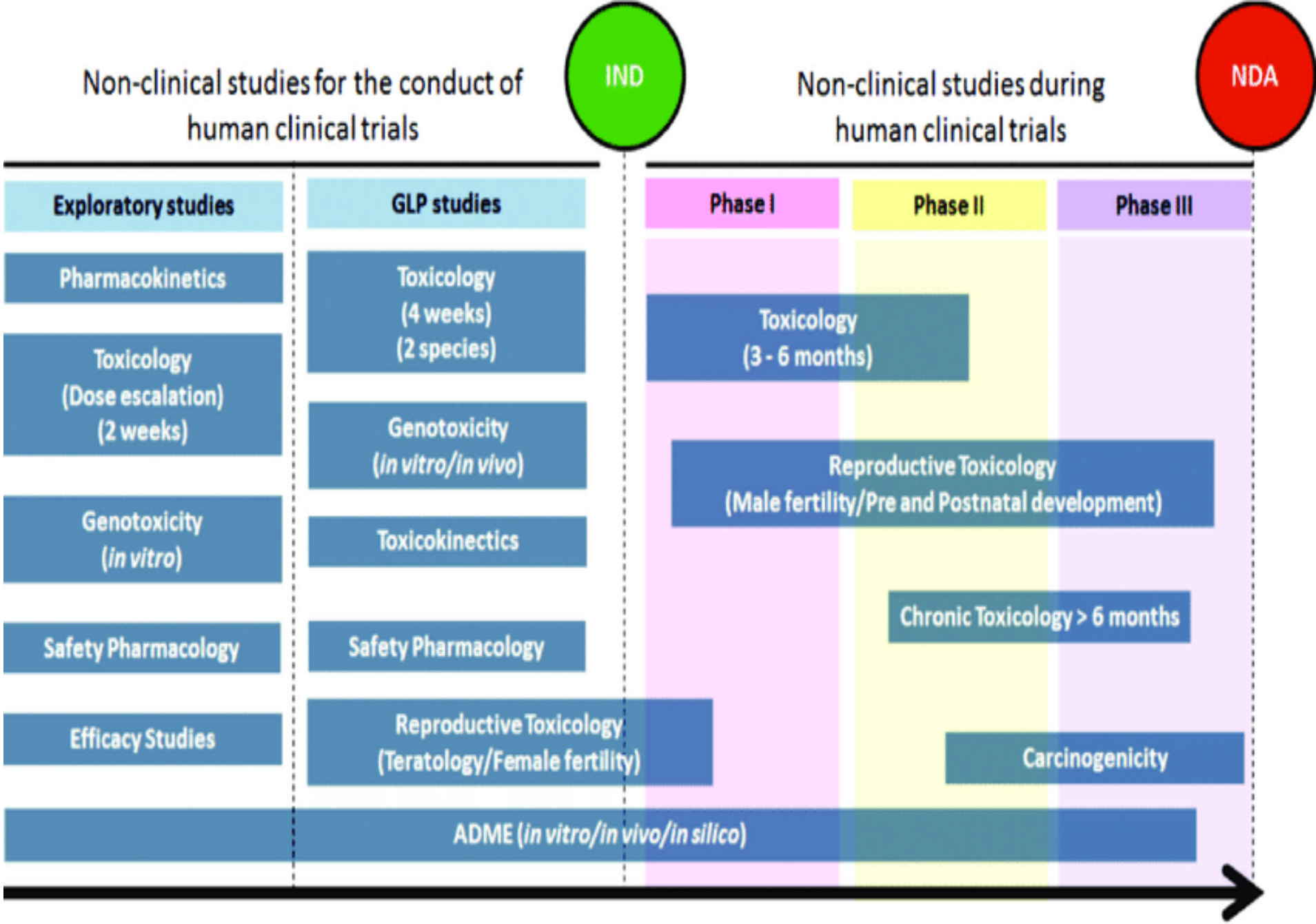
10,000 Compounds screened

250 animal testing

P1 to Approval:
13% for small molecules
32% for large molecules

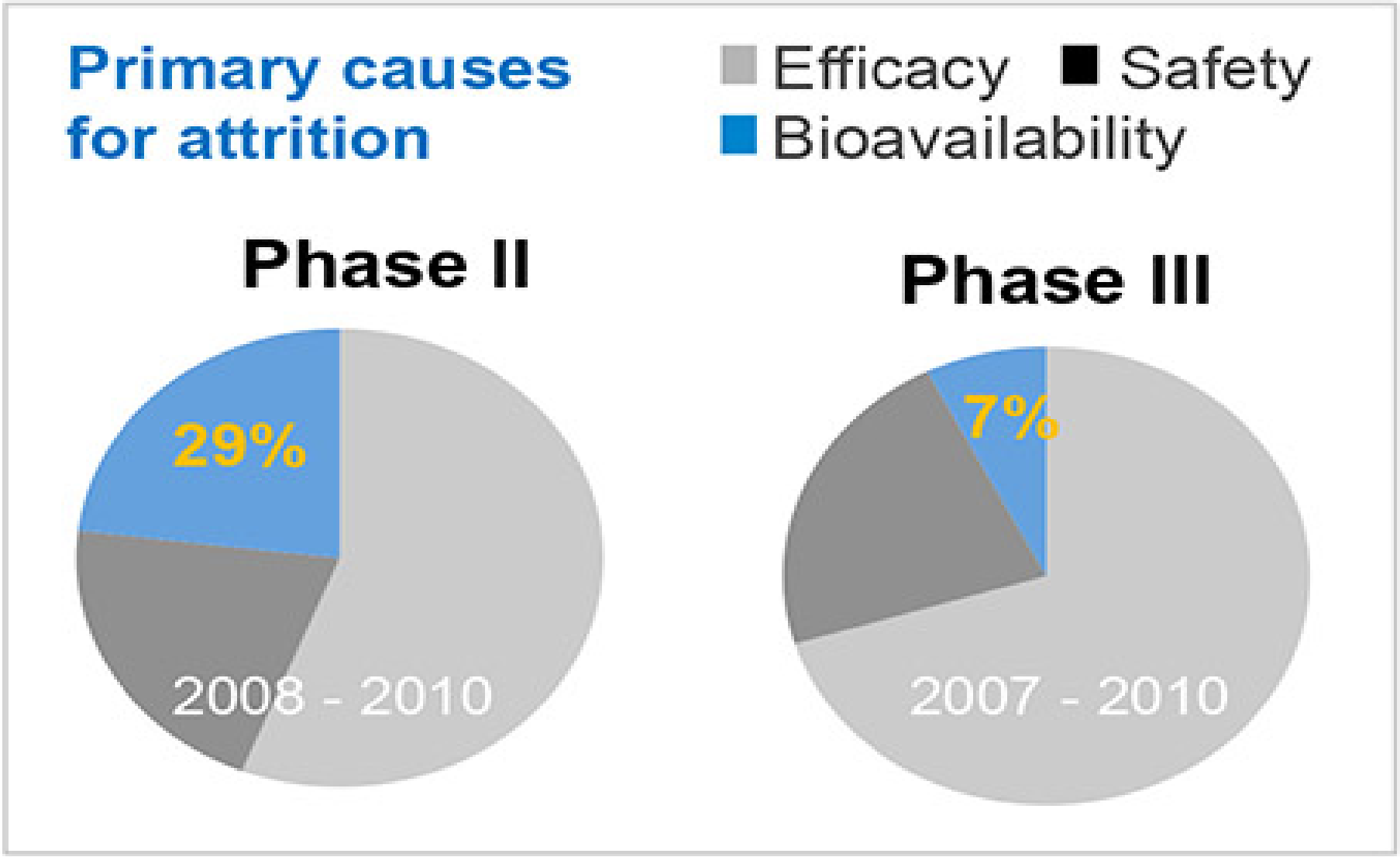
★ 1 approved drug

The estimated average pre-tax industry cost per new prescription drug approval (inclusive of failures and capital costs) is: **$2,558 million**



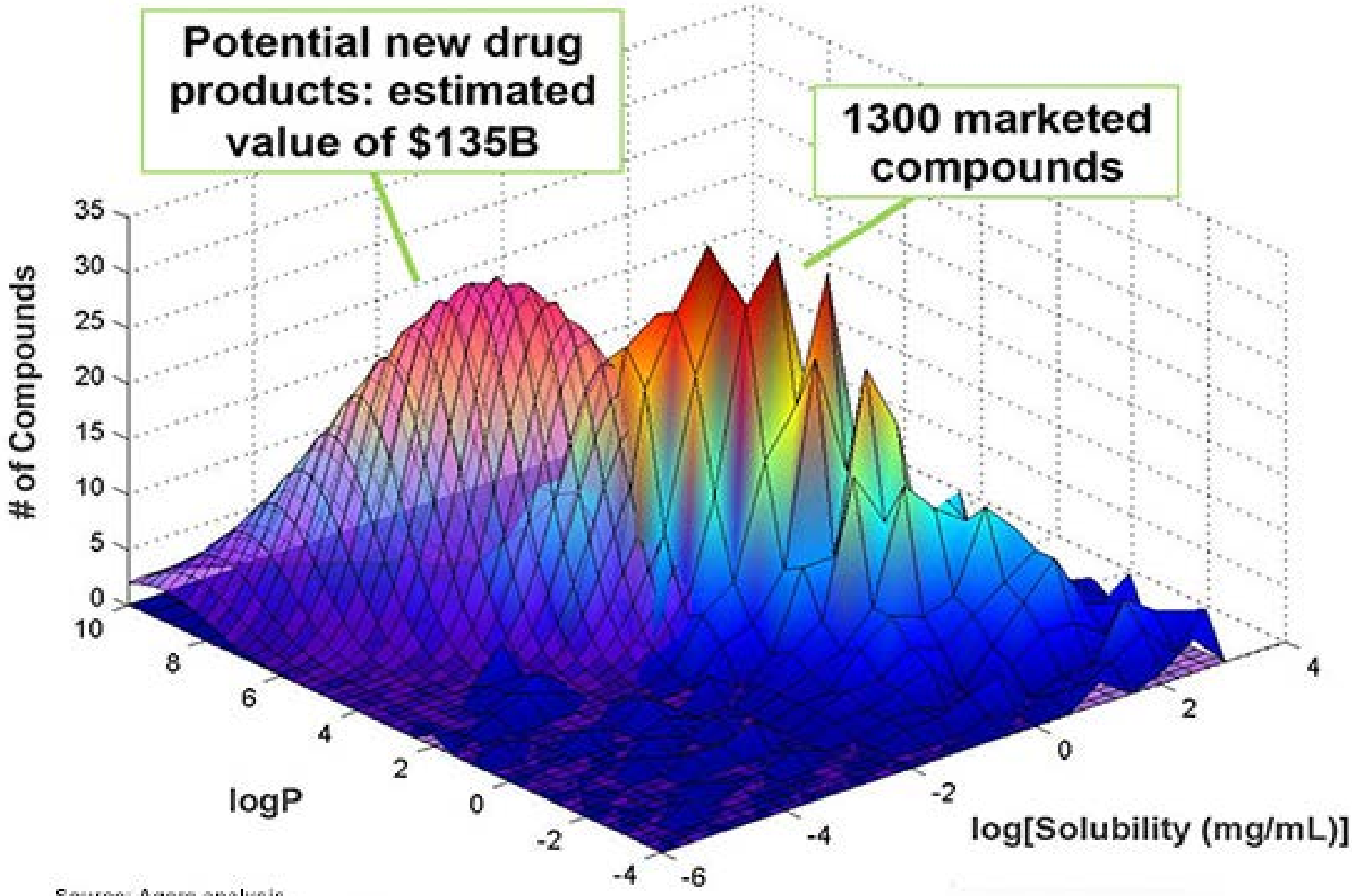
Source: Juliana Cavalli
Federal University of Santa Catarina | UFSC

Causes for Attrition: Phase II and Phase III



Source: CMR, Thomas Reuters Life Science Consulting for 2008-2010 (Phase II) and 2007-2010 (Phase III) attrition, and Agere analysis.

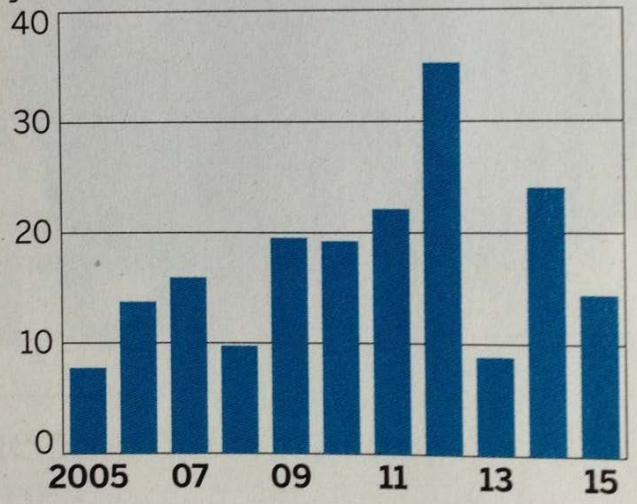
Market Opportunity: Solubilization Space



Source: Agere analysis.

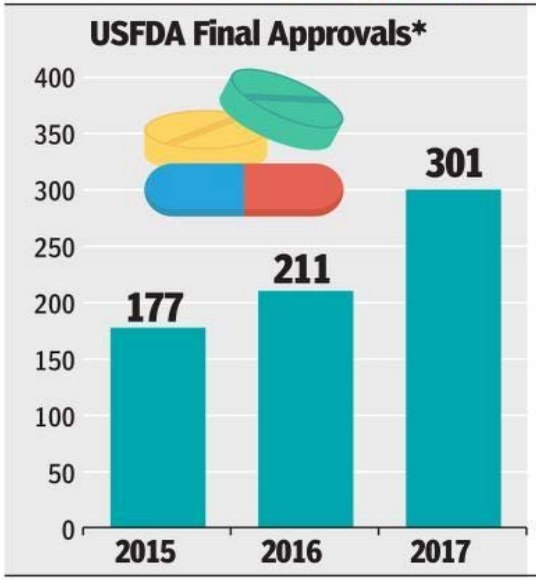
GENERICS SPIKE In the U.S., nearly $105 billion in branded-drug sales are at risk from 2011 to 2015.

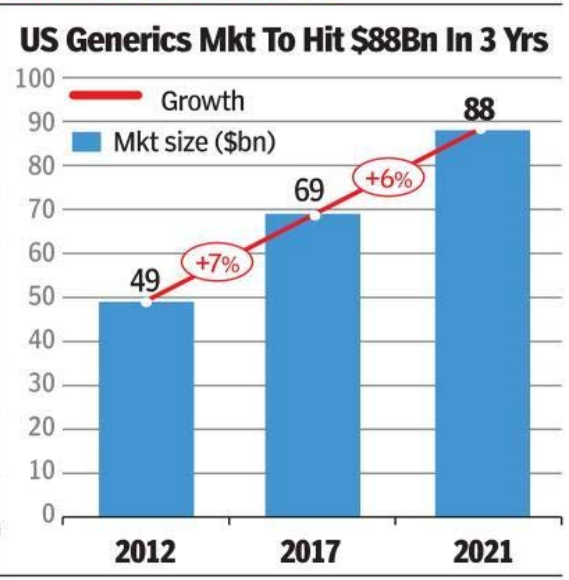
Sales of products going off patent by year-end, $ billions



NOTE: Sales for 2011 through 2015 are projected.
SOURCE: IMS Health

GETTING FORMULATION RIGHT

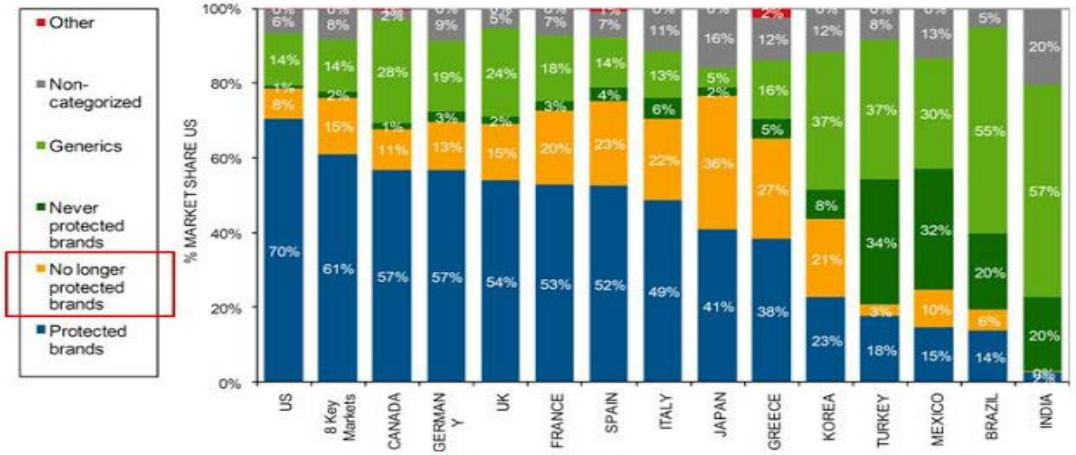




*During Jan-Dec (calendar years) Source: Industry/US FDA website

Source: IQVIA

Generics Have The Largest Share In The Pharmerging Markets



※ Source : IMS Health, MIDAS, Market Segmentation, MAT DEC 2010, Rx only

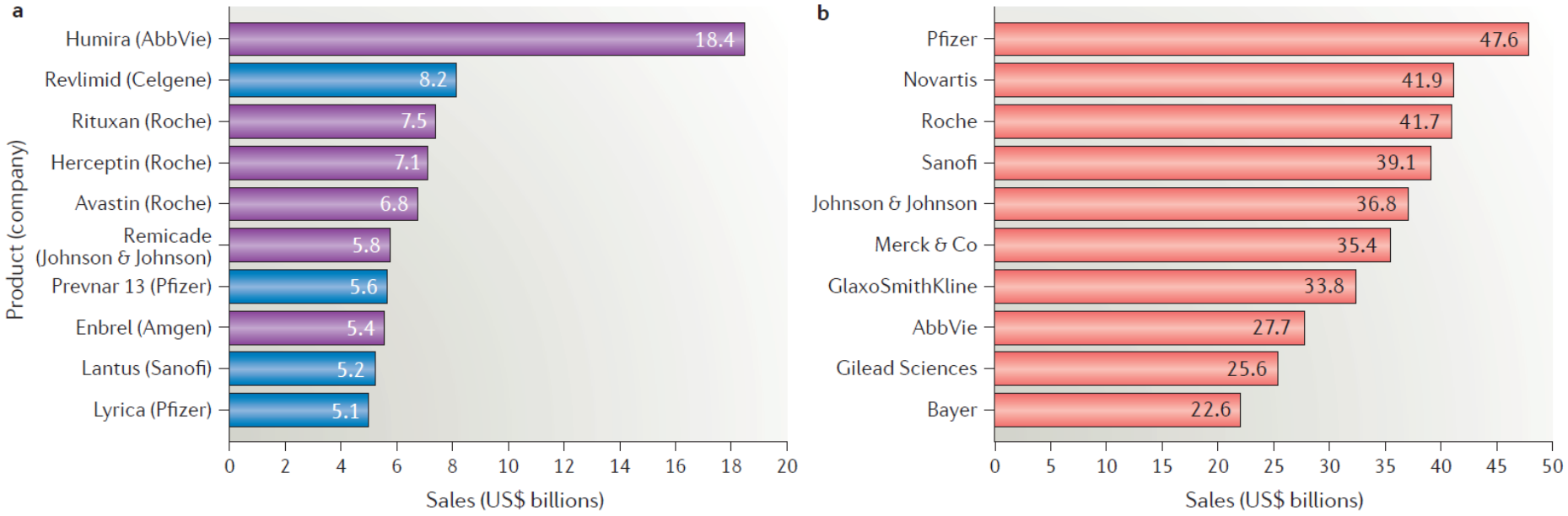
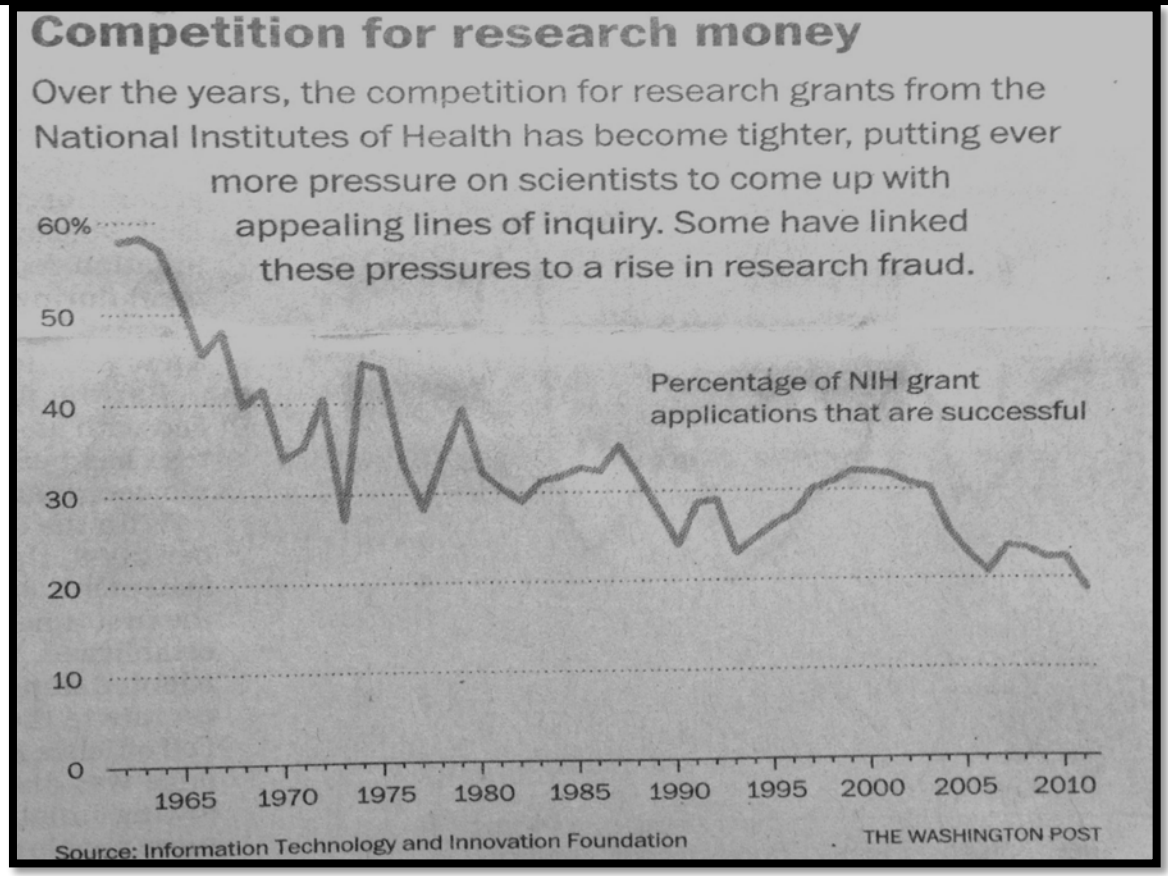


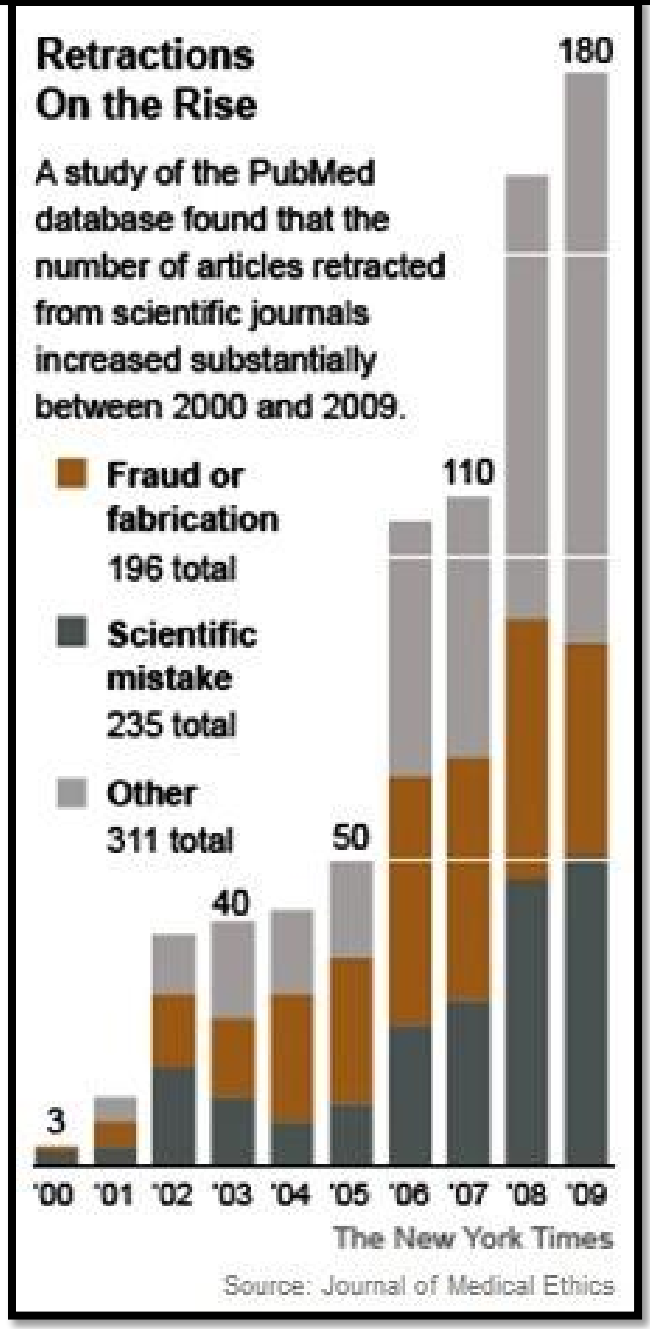
Figure 1 | **Top drugs and companies by sales in 2017. a** | Top ten drugs by sales globally, with monoclonal antibodies highlighted in purple . **b** | Top ten companies by sales of prescription and over-the-counter drugs. Source: EvaluatePharma.

Fraud in Science – Loss of Scientific Integrity



Year	Total applications	Awarded	Success rate	Average award	Total funding
2001	21,967	6,965	32%	$304,110	$8,513,561,502
2002	22,212	6,799	31%	324,325	9,362,950,132
2003	24,634	7,430	30%	340,974	10,101,683,116
2004	27,461	6,991	25%	352,214	10,555,849,413
2005	28,423	6,463	23%	361,611	10,685,232,289
2006	29,097	6,037	21%	361,307	10,522,350,609
2007	27,325	6,456	24%	362,970	10,427,770,948
2008	26,648	6,116	23%	373,804	10,429,497,662
2009	26,675	5,924	22%	391,281	10,725,000,910
2010	27,850	6,217	22%	403,691	11,125,330,616
2011	28,781	5,380	19%	408,594	10,975,655,055
2012	29,626	5,436	18%	419,321	11,021,860,936
2013	28,044	4,902	17%	405,874	10,174,867,296
2014	27,502	5,163	19%	431,177	10,359,458,392

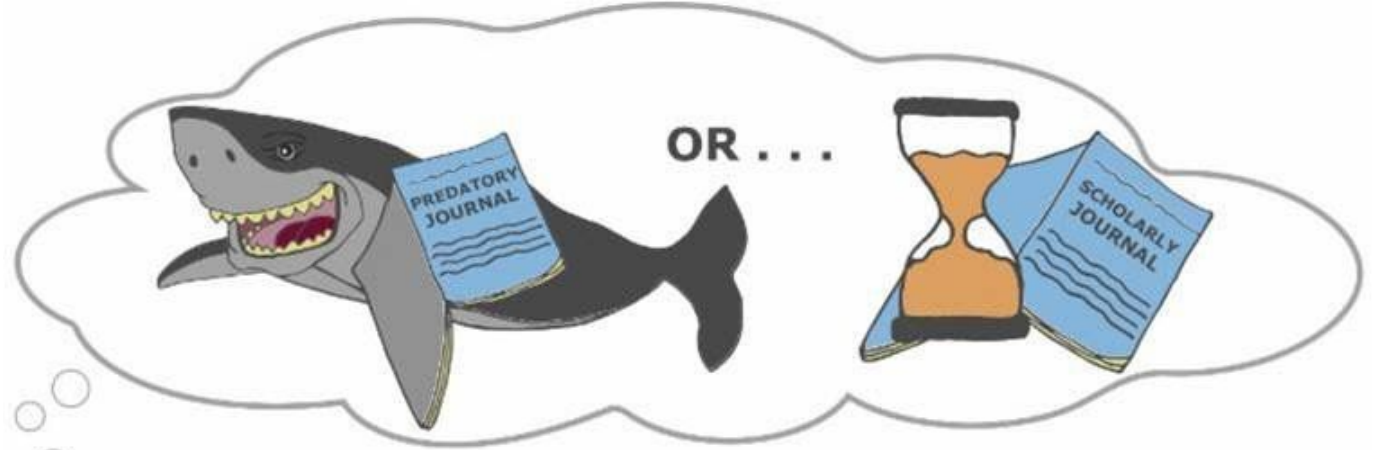
NOTE: All data are for R01 or equivalent awards: R23, R29, and R37. Actual dollars awarded without adjustment for inflation.
SOURCE: NIH Data Book

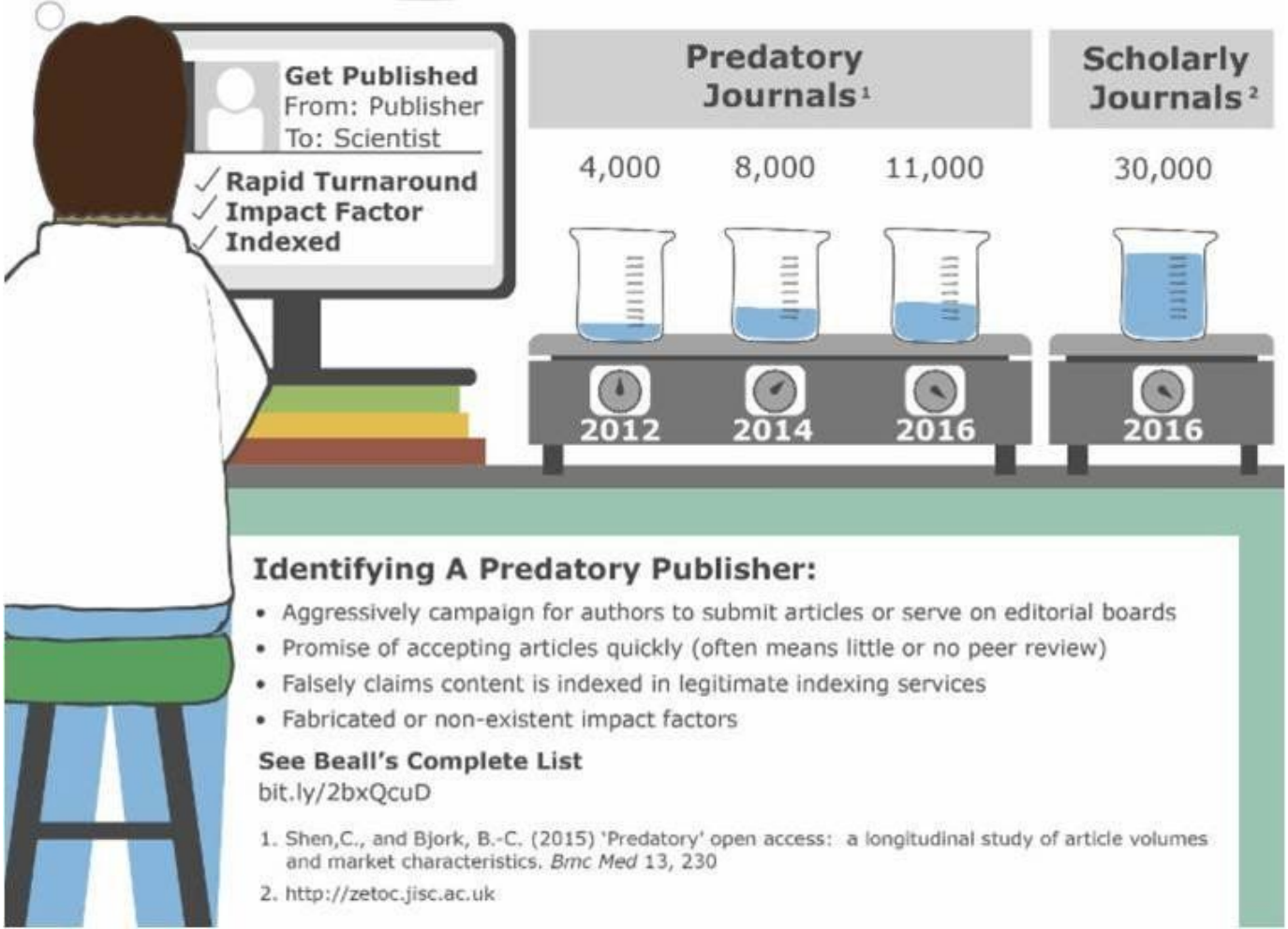


BY THE NUMBERS

18,000

The number of retracted scientific journal articles and conference abstracts dating back to the 1970s now listed in a database created by Retraction Watch and the Center for Scientific Integrity, whose mission is to promote transparency and integrity in science and scientific publishing. Most of the entries include a reason for the retraction. About 60% of the retractions were due to scientific misconduct or unethical behavior, while 40% were due to errors, reproducibility problems, and other issues, according to an analysis by *Science* (2018, DOI: 10.1126/science.aav8384).





Identifying A Predatory Publisher:

- Aggressively campaign for authors to submit articles or serve on editorial boards
- Promise of accepting articles quickly (often means little or no peer review)
- Falsely claims content is indexed in legitimate indexing services
- Fabricated or non-existent impact factors

See Beall's Complete List
bit.ly/2bxQcuD

1. Shen,C., and Bjork, B.-C. (2015) 'Predatory' open access: a longitudinal study of article volumes and market characteristics. *Bmc Med* 13, 230
2. http://zetoc.jisc.ac.uk

Chaos in Academia: Irreproducible Preclinical Research

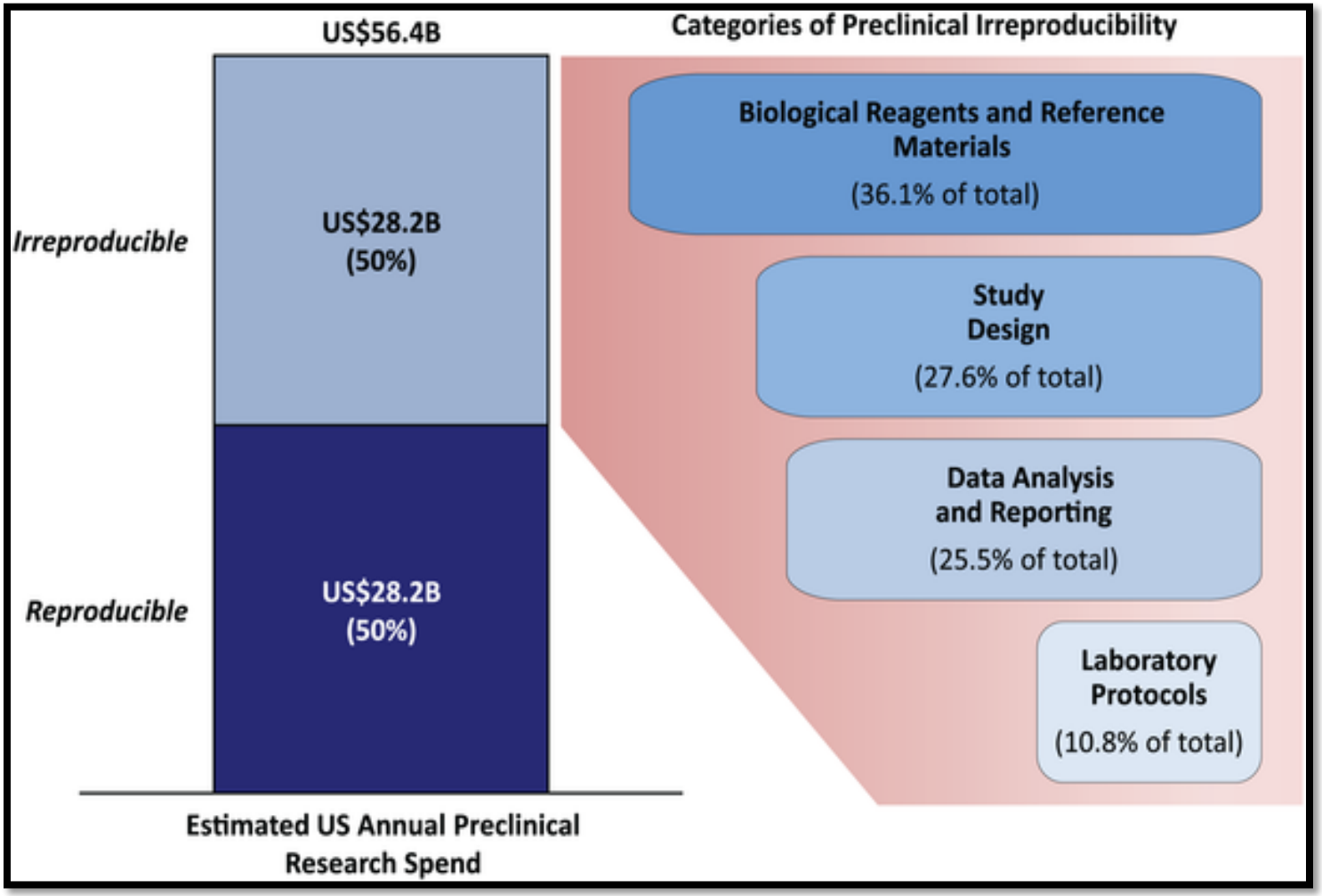


Figure 4. Economic Costs of Irreproducibility. This figure represents the estimated US preclinical research spending and categories of errors that contribute to irreproducibility. Errors in study design and biological reagents and materials contribute to a majority of the approximately US$28 billion annually spent on irreproducible preclinical research in the US. Note that the percentage value of error for each category is the midpoint of the high and low prevalence estimates for that category divided (weighted) by the sum of all midpoint error rates.

- The current pervasive culture of science focuses on rewarding flashy, eye-catching and positive findings.

- There is an increased emphasis on making provocative statements rather than presenting technical details or reporting basic elements of experimental design.

- There are reports that less than one-third of biomedical papers can be reproduced; this is due to sloppy science blamed in part on scientific culture, training and incentives.

- An unpublished survey by the American Society for Cell Biology (ASCB) in 2015 found that more than two-thirds of respondents had on at least one occasion been unable to reproduce published results.

- Drug R&D is the absence of outstanding support structure from academic drug researchers who are typically not trained to separate “hits” into compounds good, bad and ugly. Many contend that, as a result, naivety about promiscuous, assay-duping molecules is polluting the literature and wasting resources.

- Shortcuts taken by antibody manufacturers and researchers alike have resulted in a crisis of reproducibility in antibody performance.

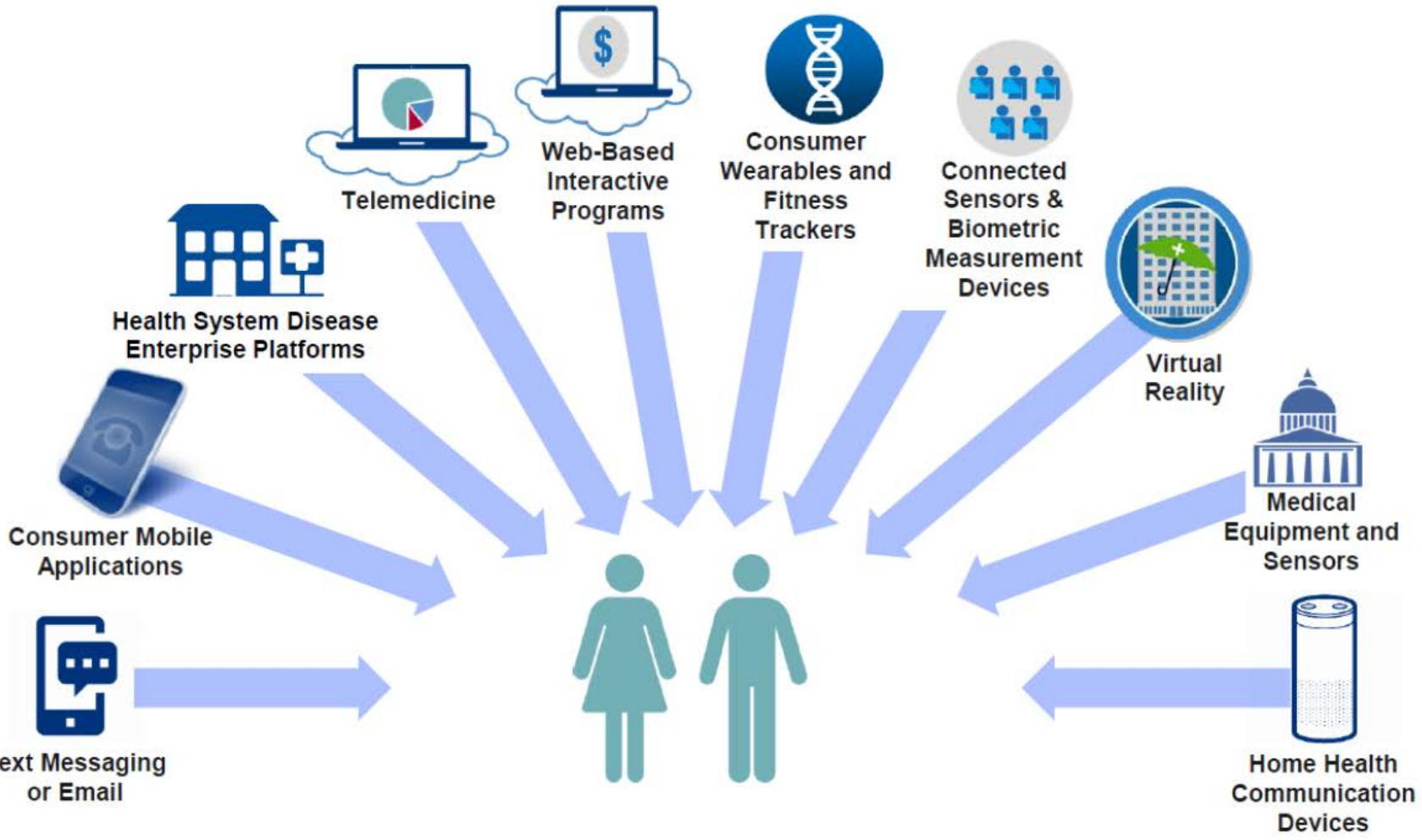
- Recently, the American Statistical Association (ASA) warned that *P* values cannot be used to determine whether a hypothesis is true or whether the results are important. According to the ASA, misuse of *P* values are also contributing to this irreproducibility crisis.

FDA Perspective

- Pharmaceutical industry: progressively greater investment and diminished return
- Biotech: success, but can society afford the products?
- Venture capital: fleeing medical products sector
- Academia: 30 year investment in biomedical research sector - will funding keep rising? What is the academic role in translational research?
- Regulators blamed for:
  - Current problems in drug development
  - Excess conservatism
  - Excess enthusiasm

Janet Woodcock, MD
Director
Center for Drug Evaluation and Research
Food and Drug Administration

Patient engagement tools are becoming more common and impacting patient care



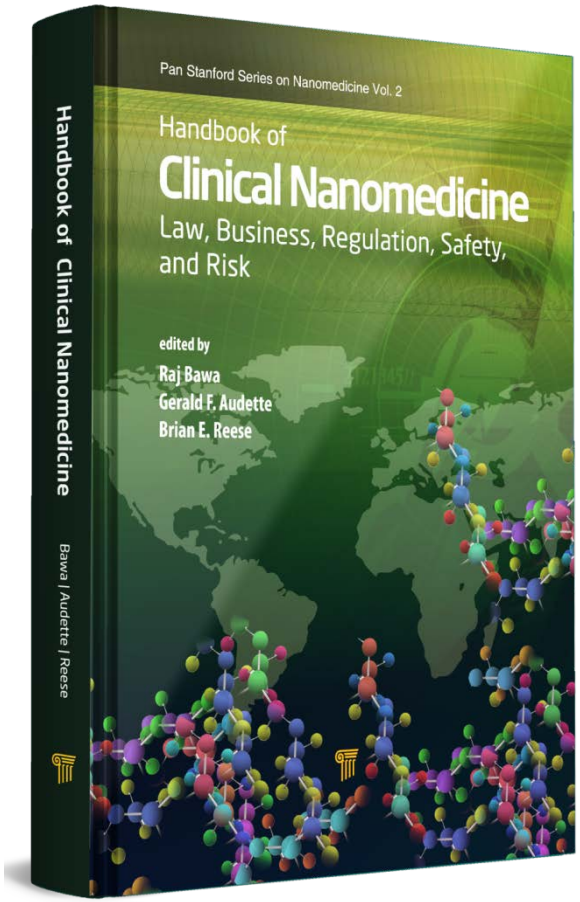
Source: QuintilesIMS Institute, Feb 2017

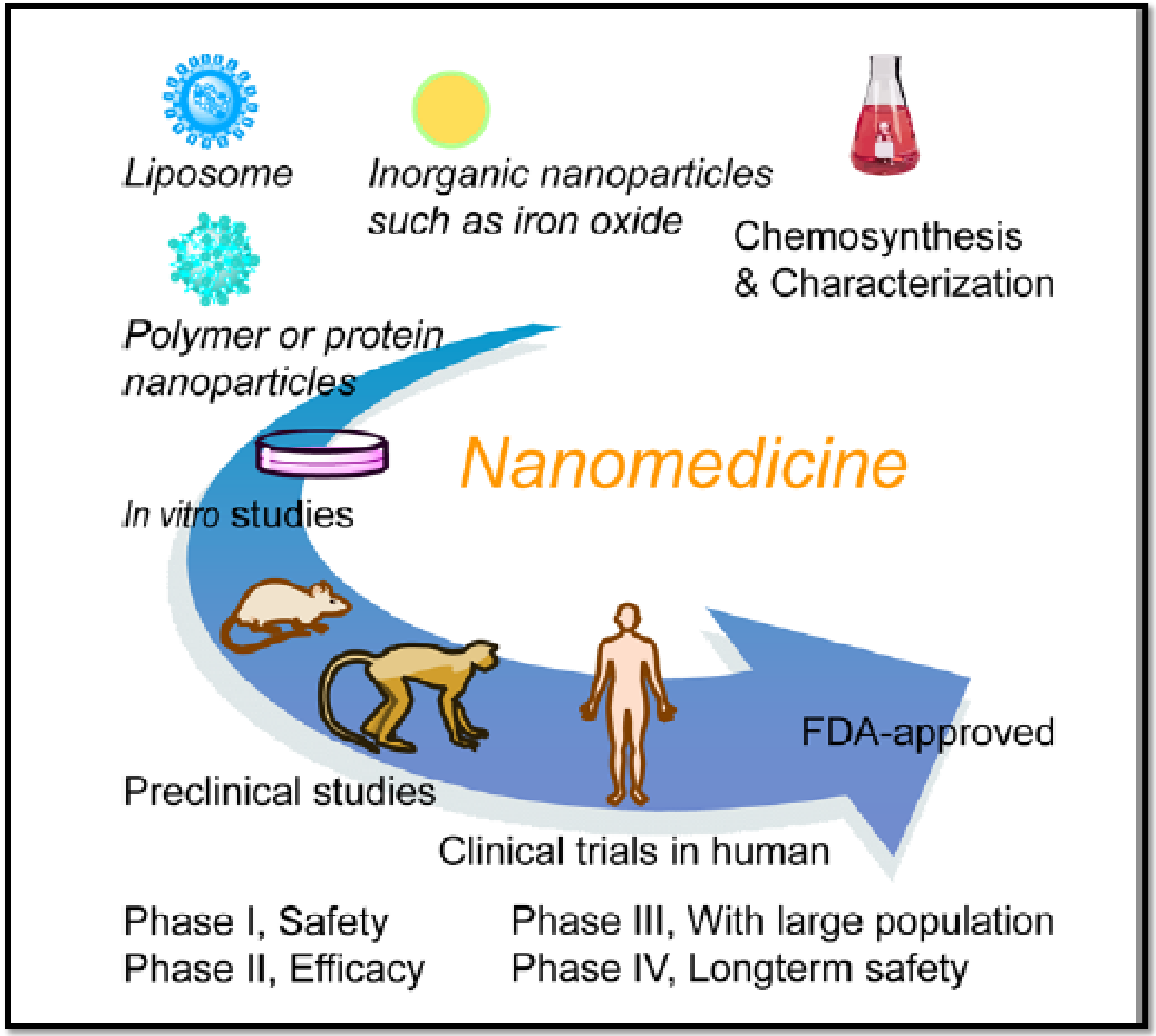
Evolving Unmet Needs in Public Health

- Shift from Acute to Chronic Conditions
- Aging Population
- Global Health Disparities
- Emerging and Re-emerging Infectious Diseases
- Emerging Non-communicable Diseases – Depression, Allergy, Obesity

Chapter 58

The Translational Challenge in Medicine at the Nanoscale[1]





Yuanzeng Min,† Joseph M. Caster,† Michael J. Eblan, and Andrew Z. Wang*

The Fundamental problem

Thanks to progress made in the biomedical sciences , the number of potential biological disease modifying targets has dramatically increased

but TRANSLATABILITY of those advances into tangible health benefits seems to have decreased

Academia, Government and Industry need to implement more innovative solutions

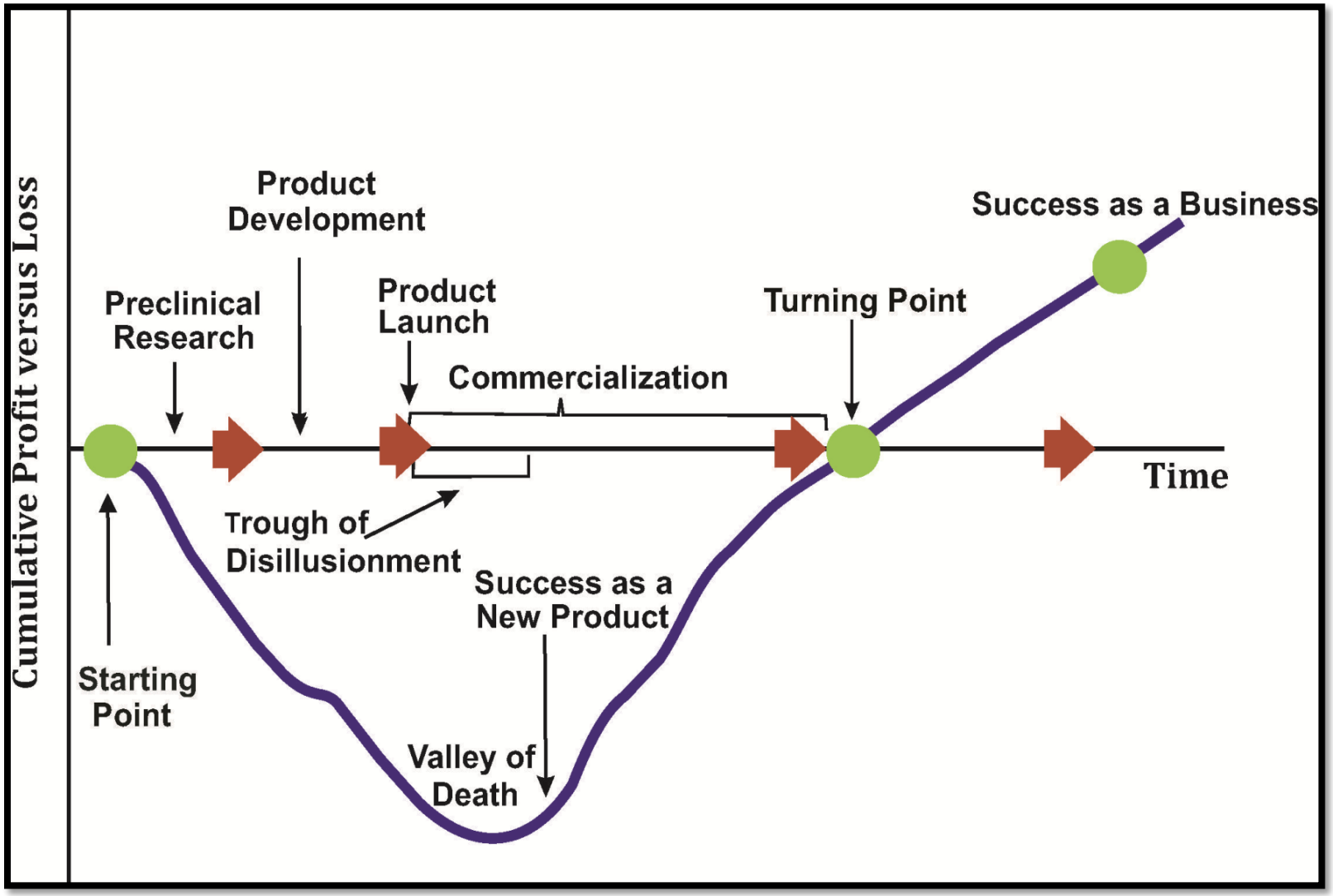
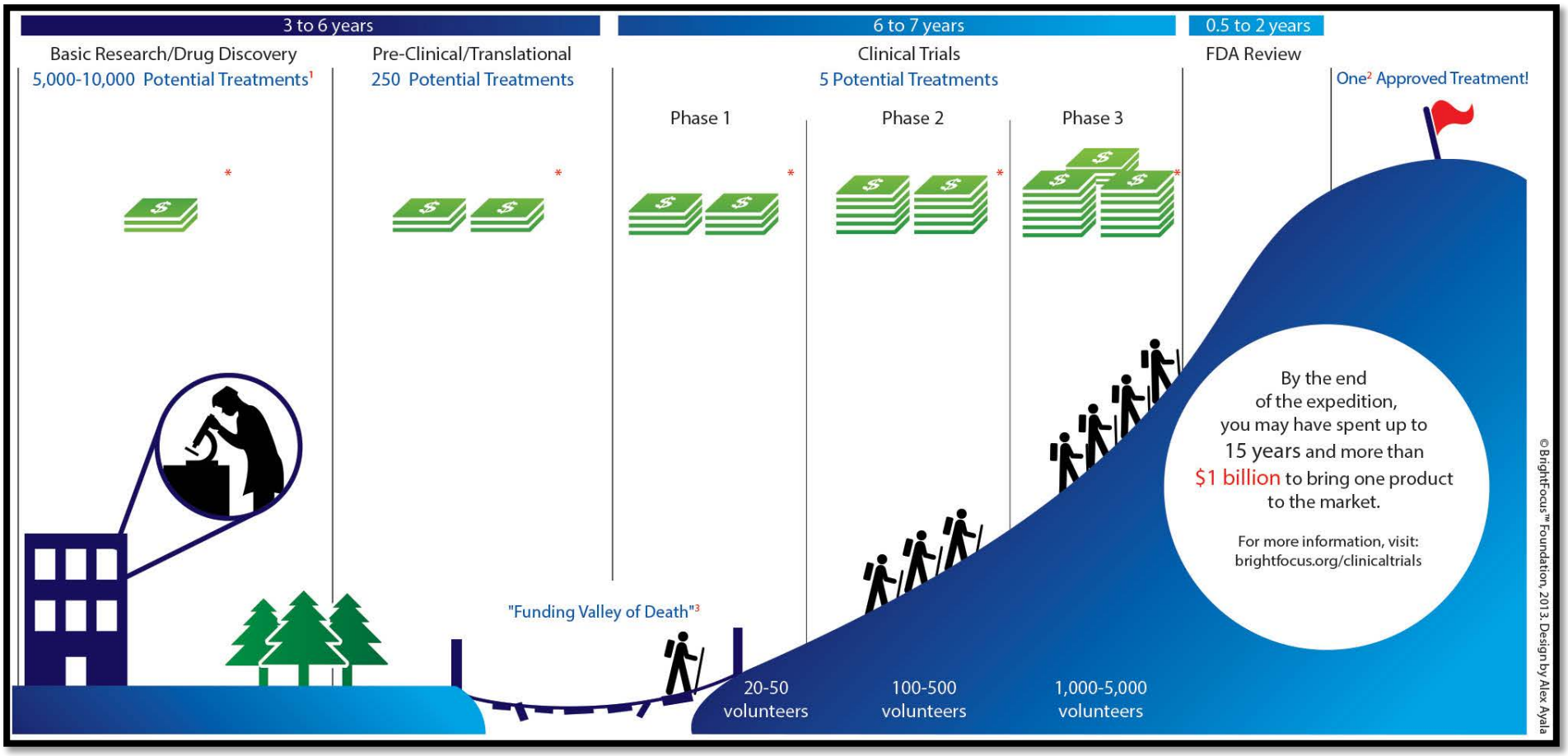


Figure 3. The Valley of Death in Commercialization. The "valley of death" represents the gap that exists between R&D breakthroughs made at the cellular and molecular biology levels on one end and the static levels of new treatments, diagnostics and preventative tools reaching the market on the other. This is the time when ideas and inventions must undergo technical feasibility review, manufacturing optimization, market demand evaluation, reduction in production costs, commercialization potential studies. This is when prior to market entry decisions are made whether to proceed or terminate product development. The *upstream* side of the valley of death (the science side) represents basic research inherently fraught with uncertainty while *downstream* (the business side) represents the more regimented process of product development characterized by manufacturing, marketing, deliverables, deadlines, budgets. Commercialization is about the translation crossing these two distinct paradigms.


3 to 6 years
6 to 7 years
0.5 to 2 years
Basic Research/Drug Discovery
5,000-10,000 Potential Treatments[1]
Pre-Clinical/Translational
250 Potential Treatments
Clinical Trials
5 Potential Treatments
FDA Review
One[2] Approved Treatment!
Phase 1
Phase 2
Phase 3
"Funding Valley of Death"[3]
20-50 volunteers
100-500 volunteers
1,000-5,000 volunteers
By the end of the expedition, you may have spent up to 15 years and more than $1 billion to bring one product to the market.
For more information, visit: brightfocus.org/clinicaltrials
© BrightFocus™ Foundation, 2013. Design by Alex Ayala

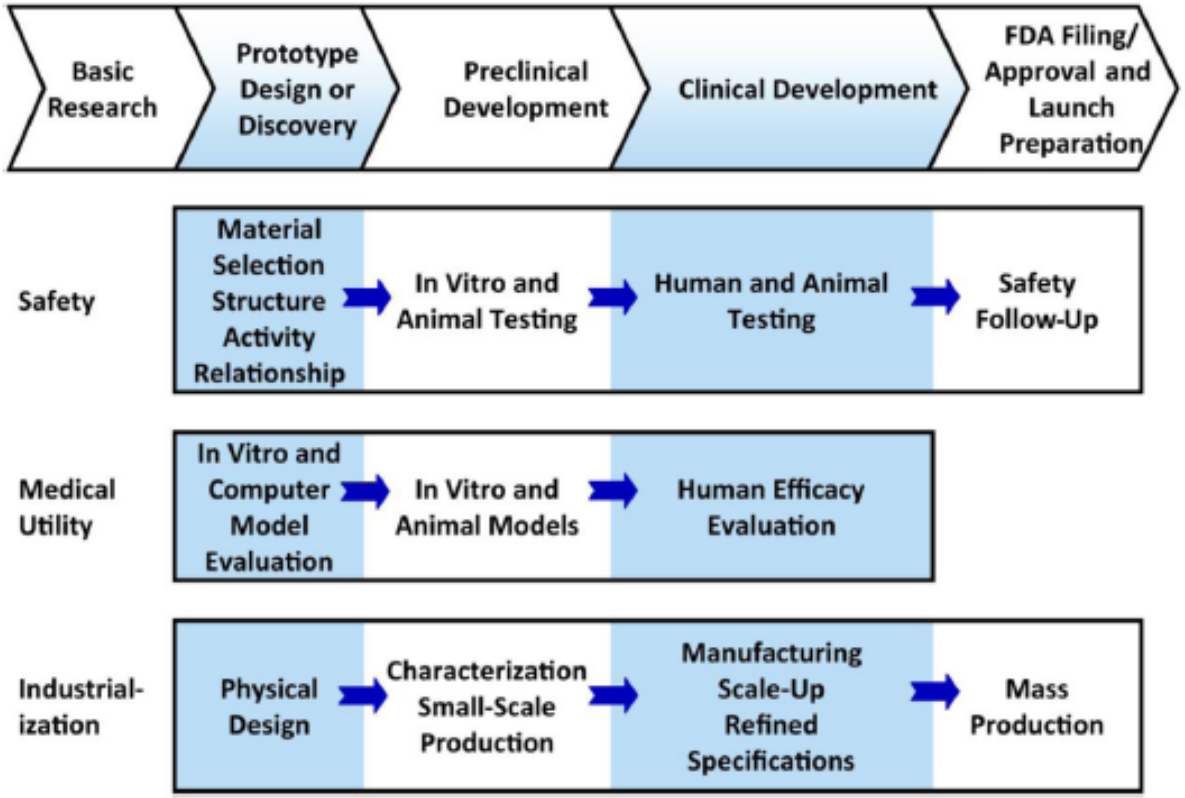
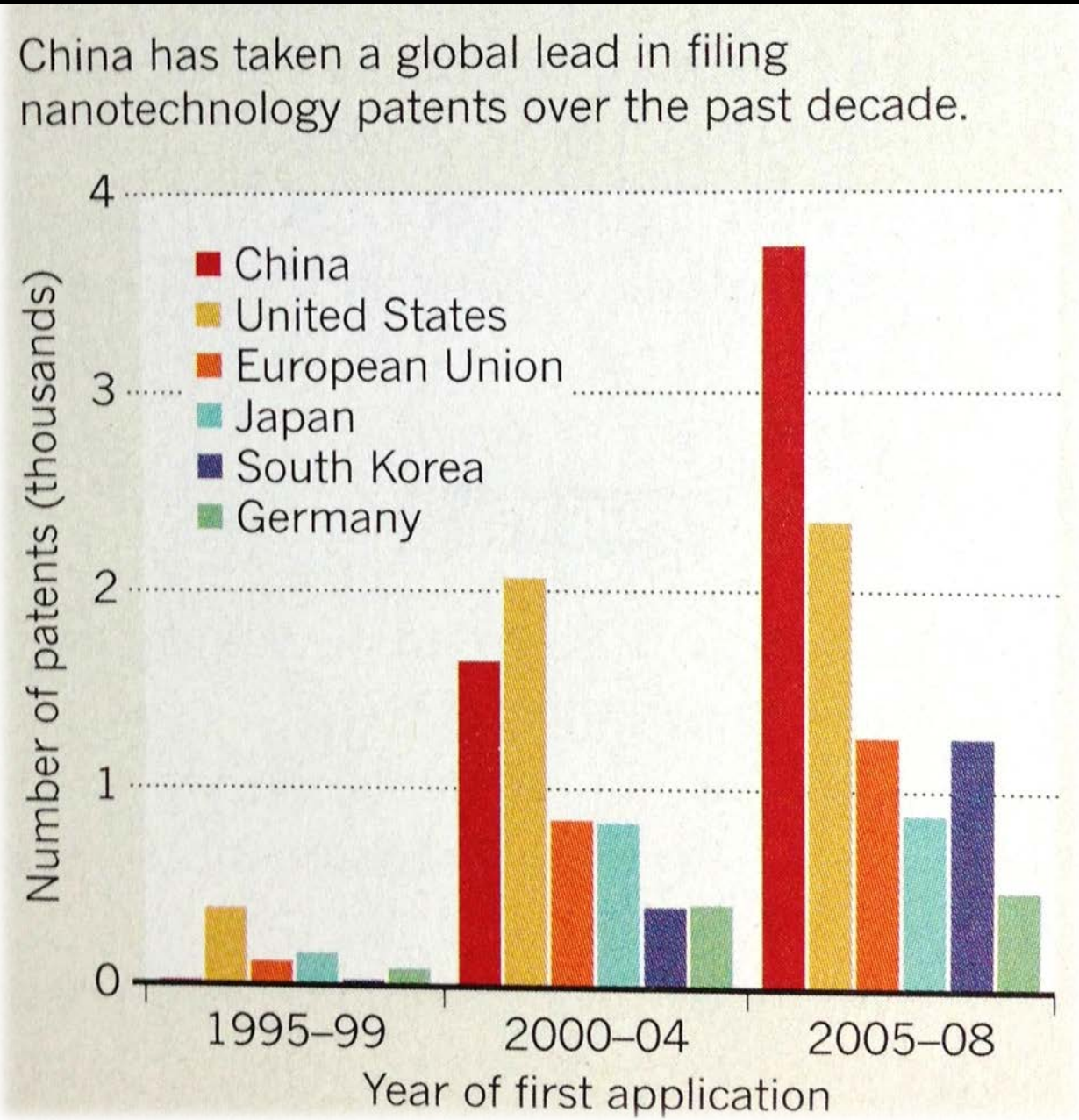


Figure 28.2 An overview of the product development pathway. This figure represents a highly generalized description of activities involving FDA-regulated product development that must be successfully completed at different points. The FDA describes three interdependent subgroups (safety, medical utility, and industrialization) of the general pathway to approval with efficiencies gained in these three subgroups affecting the overall expense and timeline to approval. In summary, development can be conceptualized as a process leading from basic research through a series of developmental steps to a commercial product. Many of the activities involving product development are highly complex and whole industries are devoted to supporting them. Not all are performed for every candidate and many activities are omitted from the figure. If the product being developed is a drug, then first a candidate drug emerges from a drug discovery program. Then, the candidate must successfully complete a series of evaluations of its potential safety and efficacy and must be amenable to mass production. For each candidate finishing the pathway, thousands of candidates are evaluated in the discovery phase. (Figure adapted from the FDA.)

Global Patent Boom? Critical?



Source: *Nature*, 2013

Pharma's Business Model

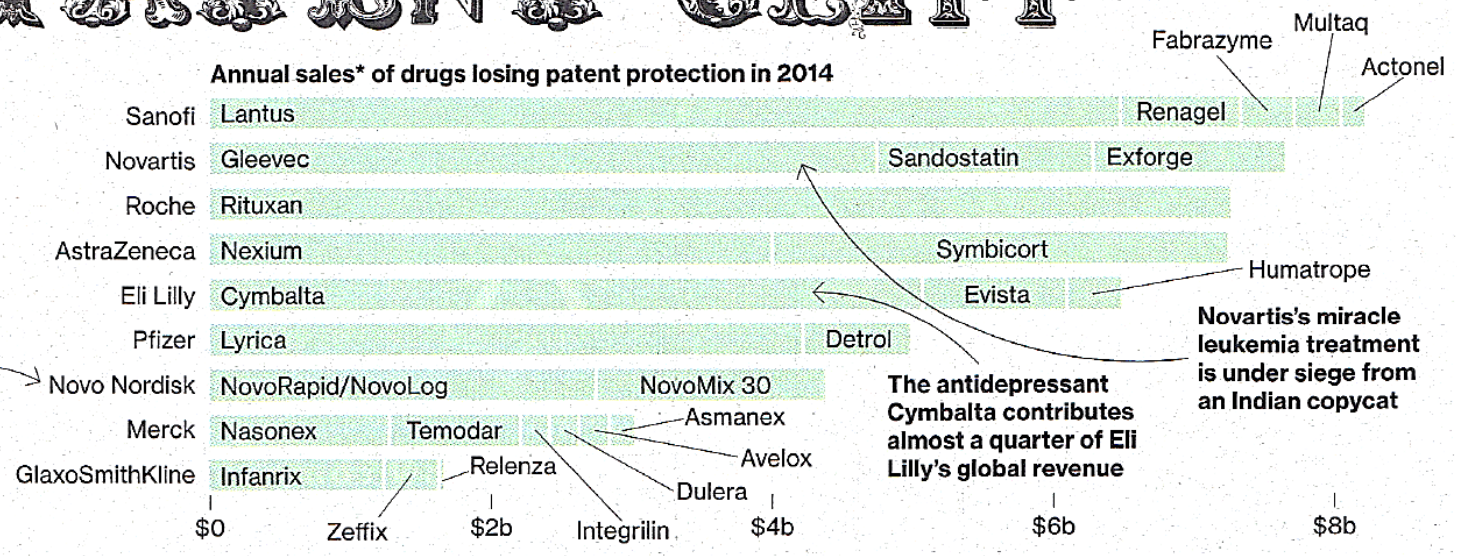
- Big pharma's business model previously relied on a few blockbusters to generate profits.
- Patent expiration on numerous blockbusters in recent years is already altering the drug landscape.
- Drug companies are also facing many other challenges that necessitate development and implementation of novel R&D strategies.
- Pharma landscape rapidly changing.

Source: Bawa (2007). Patents and nanomedicine. *Nanomedicine* 1(2):150-158.

THE PATENT CLIFF

Drugs going off-patent in 2014 contribute just under $50 billion in pharmaceutical industry revenue. Not all products losing protection face imminent competition from generics; biological products and drugs delivered by devices are best poised to extend their money-spinning streak.

Annual sales* of drugs losing patent protection in 2014



It's not as bad as it looks—Novo Nordisk's insulin pens are harder to replicate than a pill

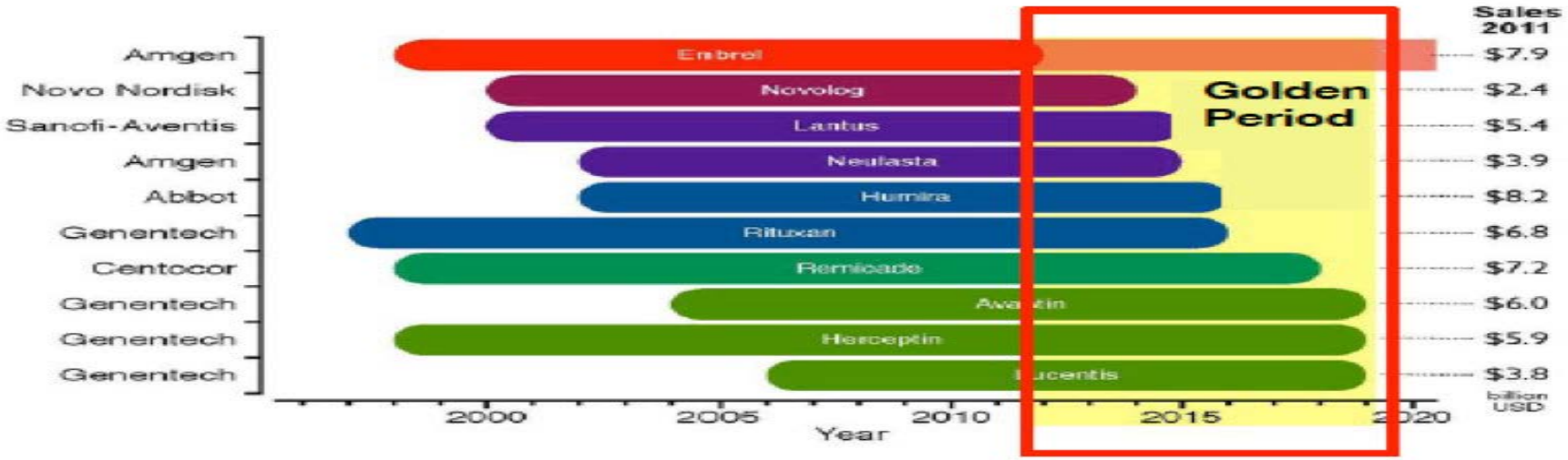
The antidepressant Cymbalta contributes almost a quarter of Eli Lilly's global revenue

Novartis's miracle leukemia treatment is under siege from an Indian copycat

*ESTIMATES ARE BASED ON GLOBAL FISCAL 2012 SALES FOR EACH DRUG. GRAPHIC BY BLOOMBERG BUSINESSWEEK. DATA: BLOOMBERG INDUSTRIES

Courtesy: *Bloomberg*, November 2013

Top 10 Selling Biologic's Patent Cliff

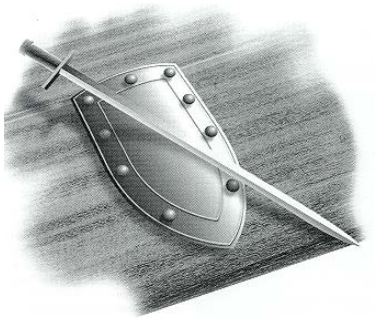


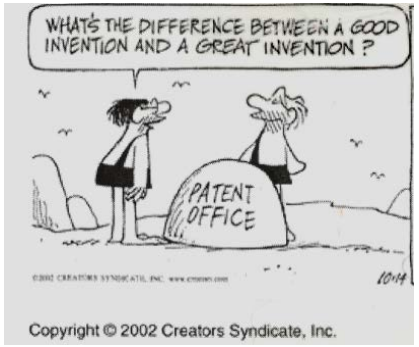
Calo-Fern´andez B et al (2012) Pharmaceuticals 2012, 5, 1393-1408

What is a Patent?

"If a man can...make a better mousetrap, though he builds his house in the woods, the world will make a beaten path to his door."
-- Ralph Waldo Emerson in an 1871 lecture

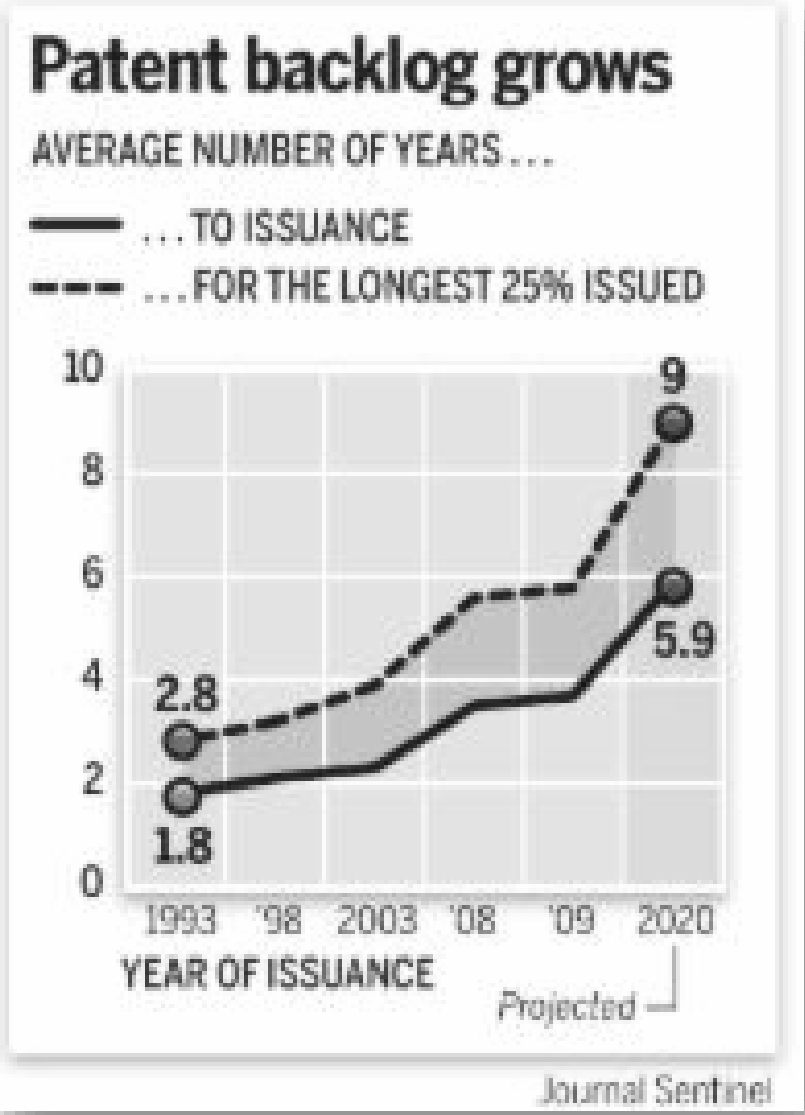
- **A US patent is a legal document granted by the federal government whereby the recipient (or "patentee") is conferred the temporary right (limited monopoly) to exclude others from:**
  making,
  using,
  selling,
  offering for sale, or
  importing into the US the invention for up to 20 years from the filing date.

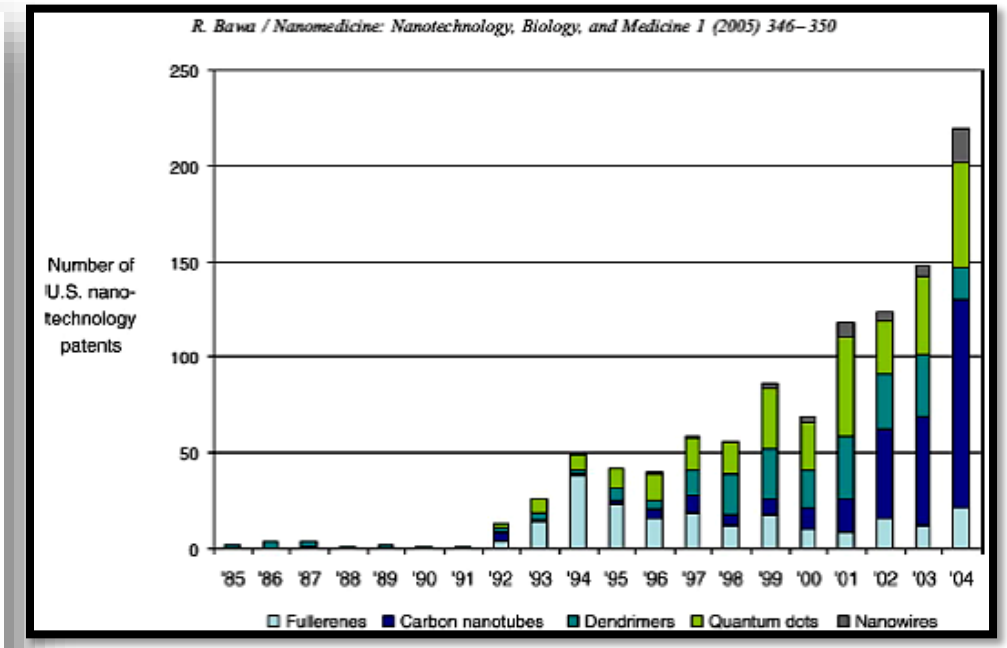




- **A US patent provides protection only in the US and its territories.**
- **Does not grant the owner/inventor the right to use his invention**
- **Monopoly is in return for full disclosure to the public**
- **Patent can be licensed, assigned or conveyed**
- **Basis of US patent system in the constitution - Thomas Jefferson**

Patent Office Swamped by Backlog

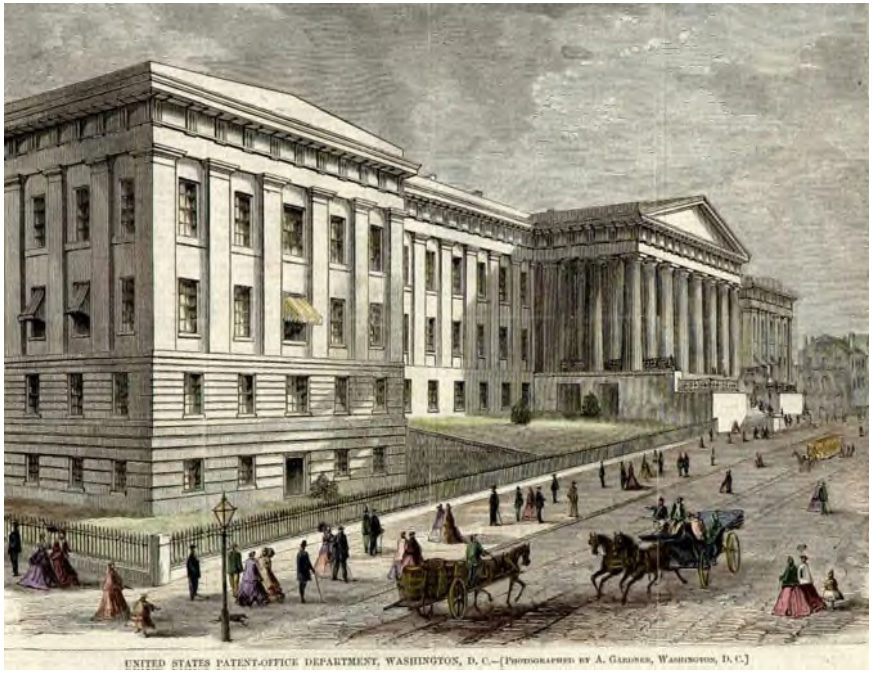




Crisis at the US Patent Office

Preliminary Classification System (only a rough estimate)
High Attrition/New Patent Examiners (~1200+ in ’07 alone)
Funding Issues (Congress-PTO Issues)
Patent Pendency (According to PTO - 25.4 to 44 months)
Pending (in ’07 - 700000 unexam.; 300000 examined)
Industry-PTO Interaction (Much More)
Training/Guidelines (Even More Needed)
Access to Non-patent Prior Art (Problems?)
Quality/Allowance Rate (77-95% vs. 54%)

Homes of the US Patent Office



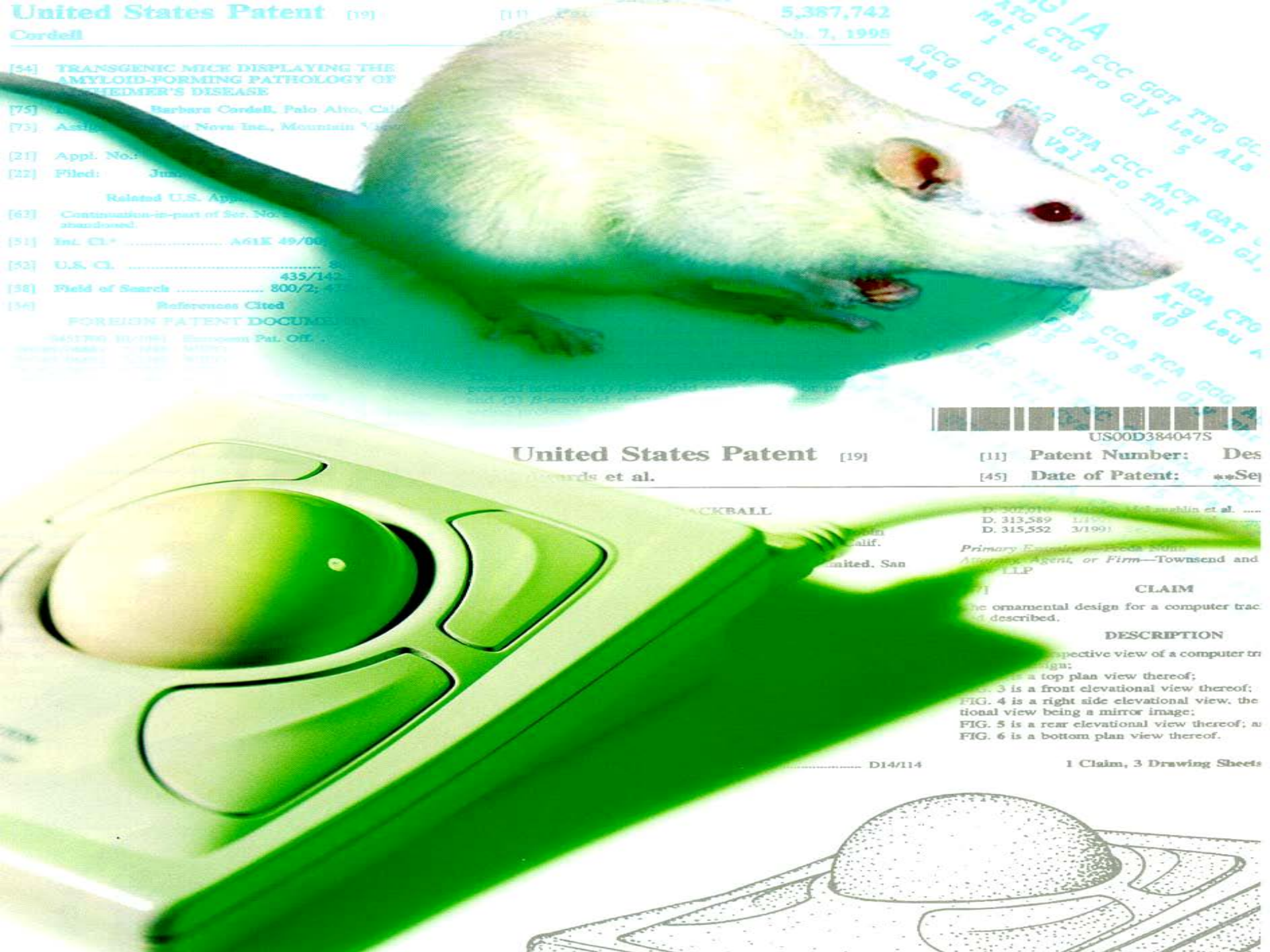
**SLEEPING-BUNKS OF THE FIRST RHODE ISLAND REGIMENT,
AT THE PATENT OFFICE, WASHINGTON.**

Einstein in the Bern patent office. "A practical profession is a salvation for a man of my type; an academic career compels a young man to scientific production, and only strong characters can resist the temptation of superficial analysis."

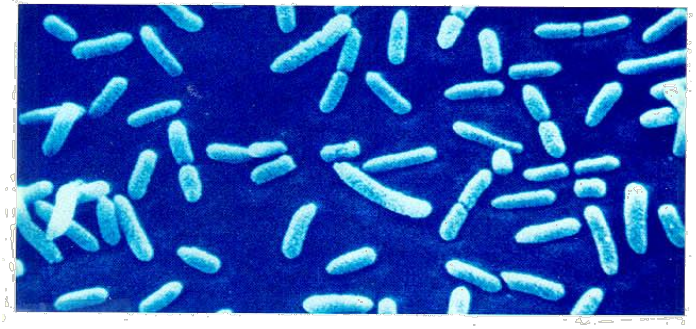
P.J. Federico

"[U]nder section 101 a person may have invented a machine or manufacture, which may include *anything under the sun that is made by man*."

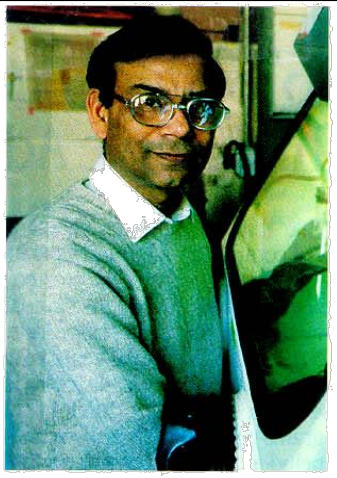
–Hearing on H.R. 3760 before Subcommittee No. 3 of the House Committee on the Judiciary, 82d Cong., 1st Session, 37 (1951)


United States Patent [19]
Cordell
5,387,742
Feb. 7, 1995
[54] TRANSGENIC MICE DISPLAYING THE AMYLOID-FORMING PATHOLOGY OF ALZHEIMER'S DISEASE
[75] Barbara Cordell, Palo Alto, Calif.
[73] Assignee: Athena Neuro Inc., Mountain View, Calif.
[21] Appl. No.:
[22] Filed: Jun.
Related U.S. Application Data
[63] Continuation-in-part of Ser. No. abandoned.
[51] Int. Cl.* A61K 49/00
[52] U.S. Cl. 435/142
[58] Field of Search 800/2;
[56] References Cited
FOREIGN PATENT DOCUMENTS
European Pat. Off.
US00D384047S
United States Patent [19]
et al.
[11] Patent Number: Des
[45] Date of Patent: **Sep
D. 313,589 1/199
D. 315,552 3/199
Primary Examiner—Freda Nolin
Attorney, Agent, or Firm—Townsend and
LLP
CLAIM
The ornamental design for a computer trac
described.
DESCRIPTION
spective view of a computer tr
sign;
a top plan view thereof;
3 is a front elevational view thereof;
FIG. 4 is a right side elevational view, the
tional view being a mirror image;
FIG. 5 is a rear elevational view thereof; a
FIG. 6 is a bottom plan view thereof.
1 Claim, 3 Drawing Sheets

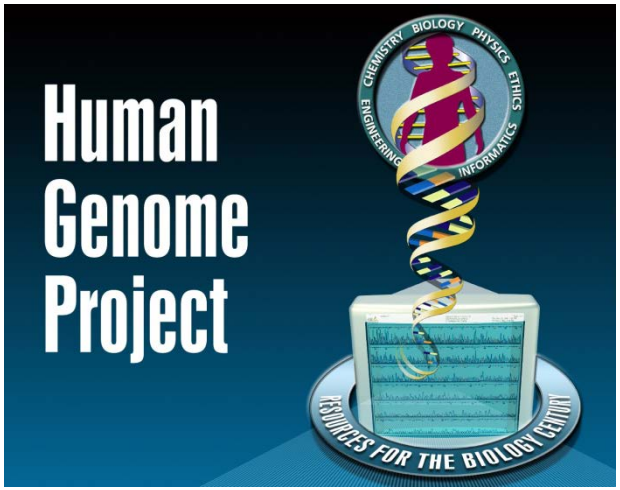
Patenting Life

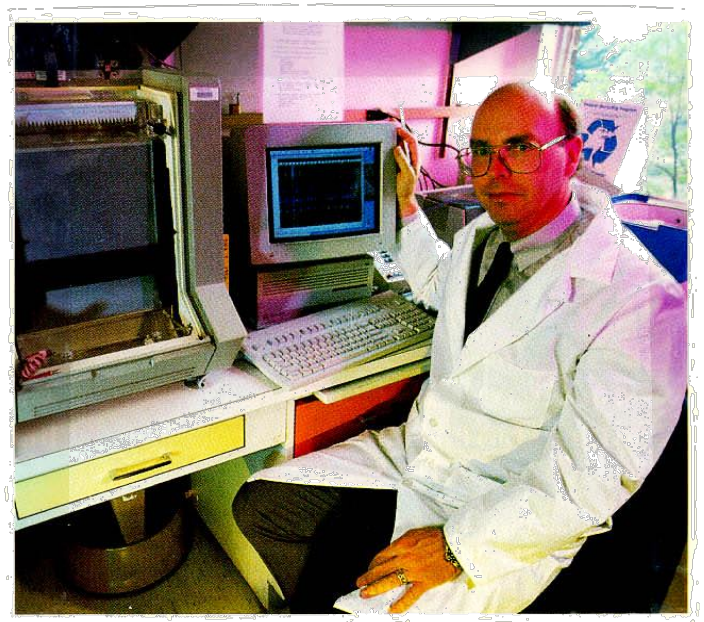


OIL-EATING BACTERIA were the first organisms to be protected under a standard U.S. patent. They were developed as a possible means of cleaning up oil spills.



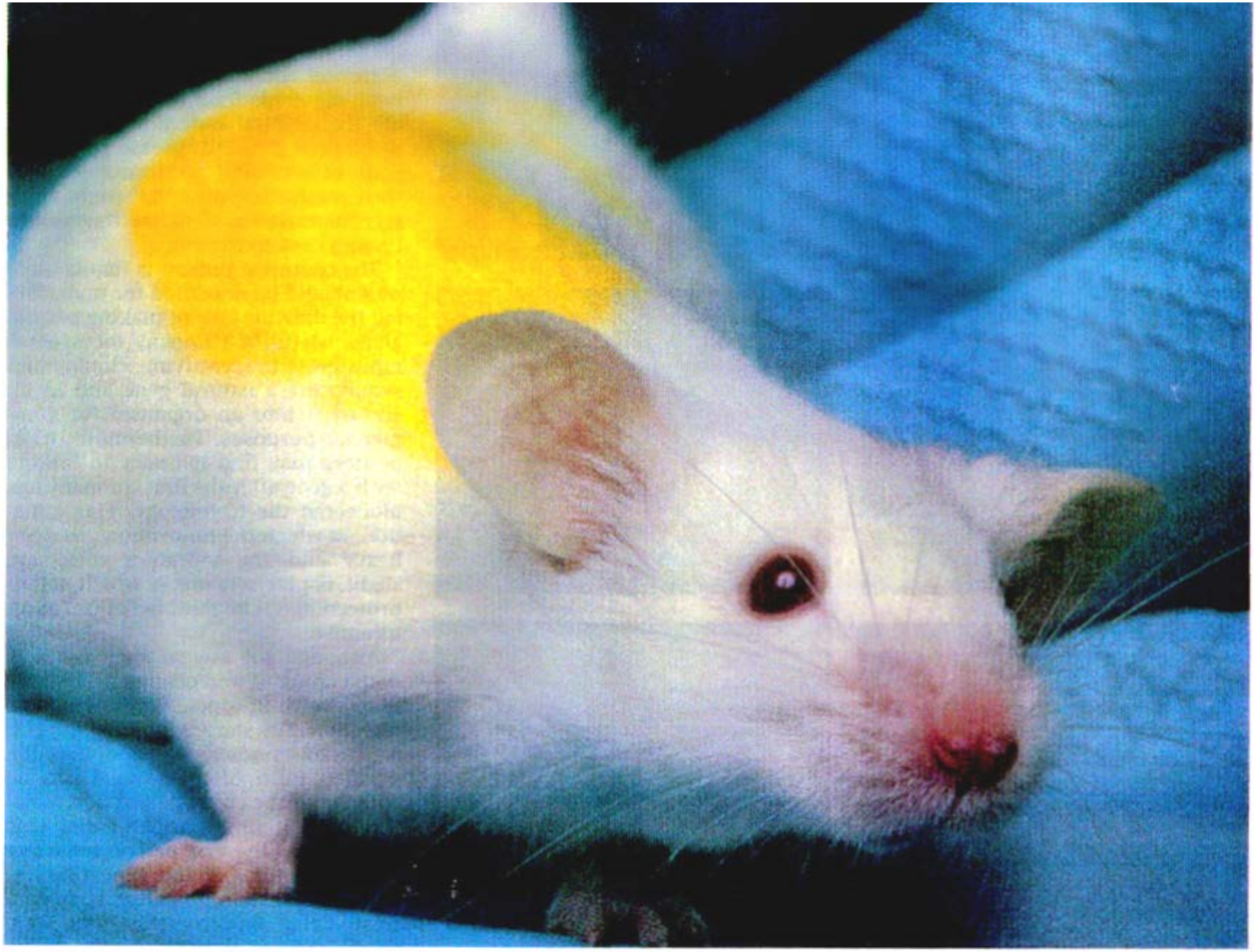
ANANDA M. CHAKRABARTY won the first patent on an altered life-form in June of 1980. Photograph by Valentina von Schacht.





J. CRAIG VENTER with DNA sequencing machine, one of seven in his laboratory that are tagging human genes. Photo: Randy Santos/Randolph Photography.

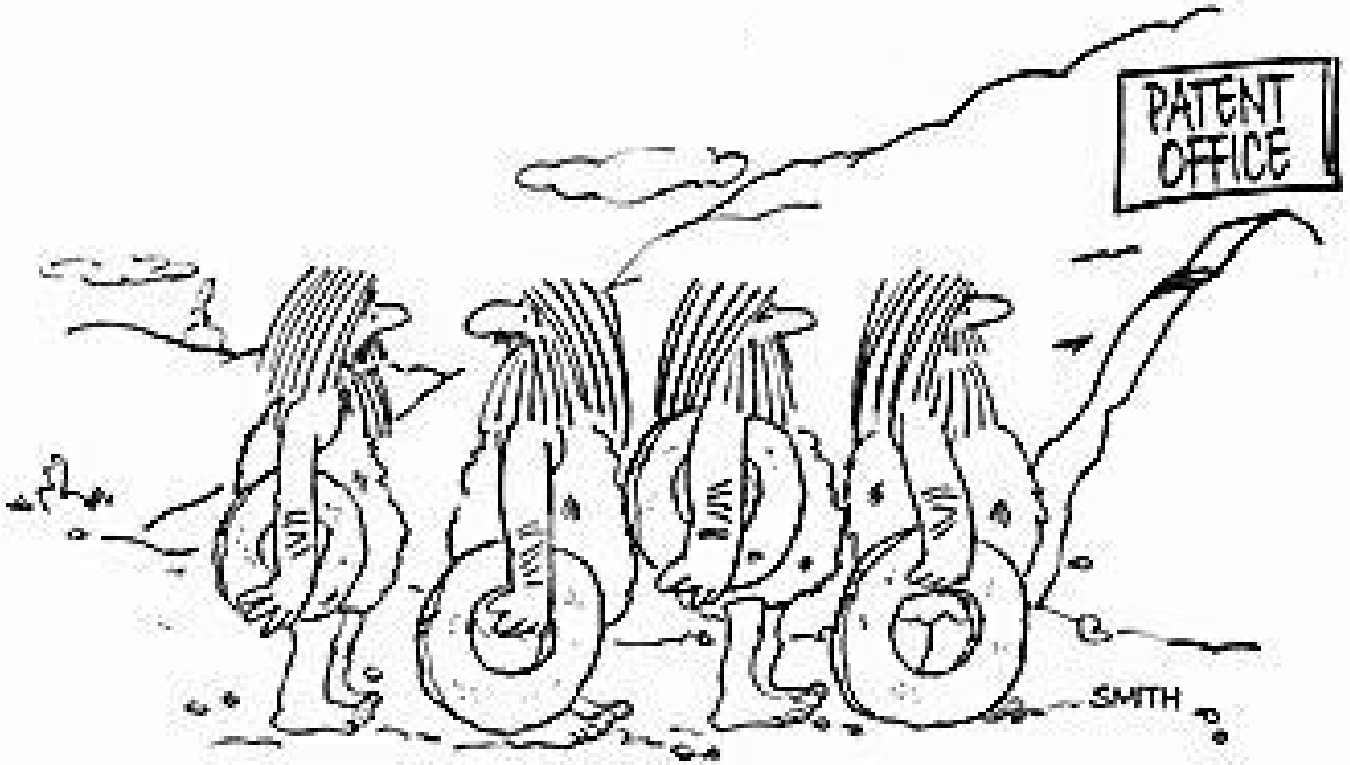
Patenting Animals - The Harvard Mouse



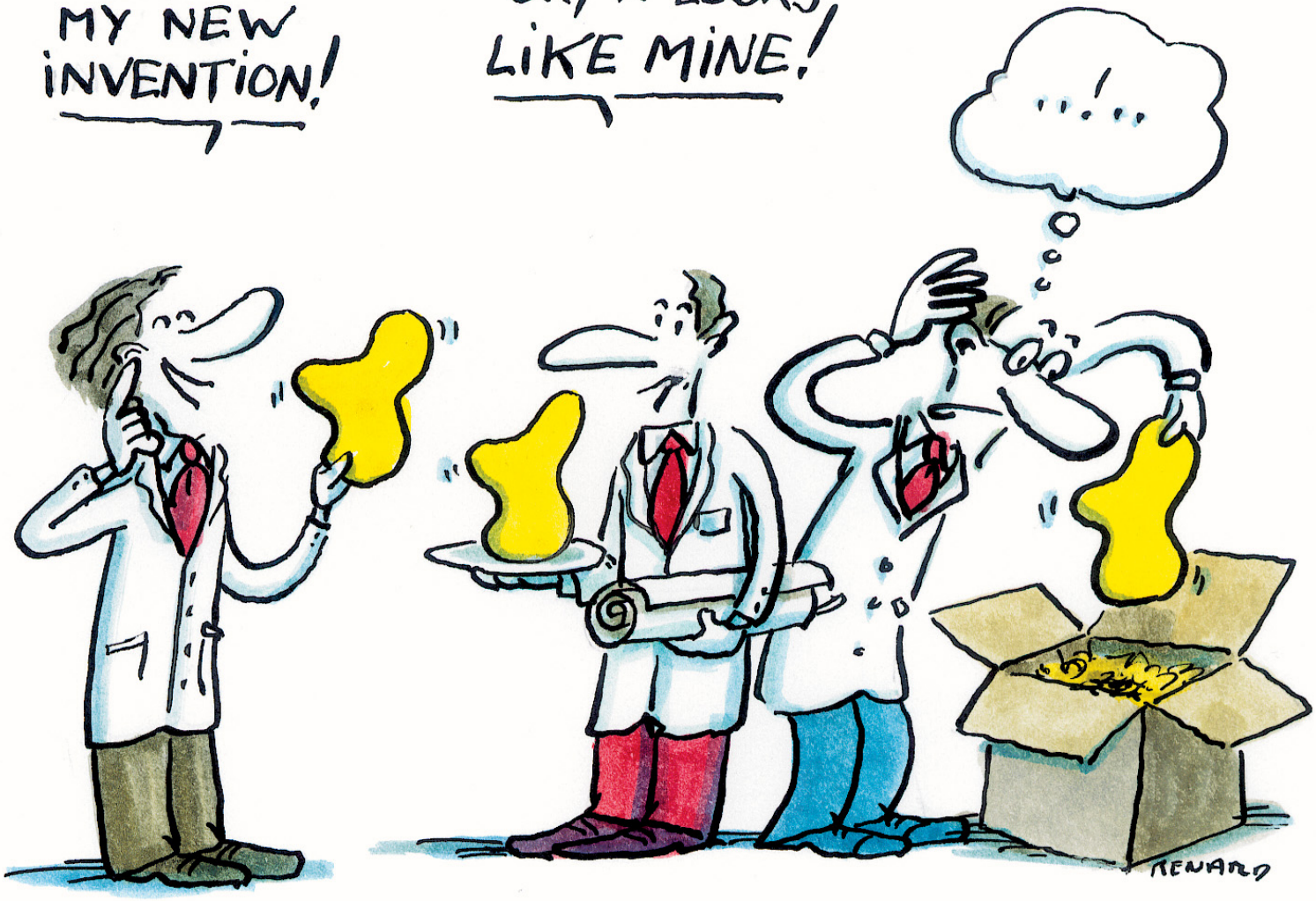
GENETICALLY ENGINEERED MOUSE carries a human cancer gene that makes it valuable for medical research. In 1988 such mice became the first [redacted] animals protected by a U.S. patent. More patents on animals can be expected as transgenic experiments continue. The yellow spot of dye on the mouse's back is an identification mark.

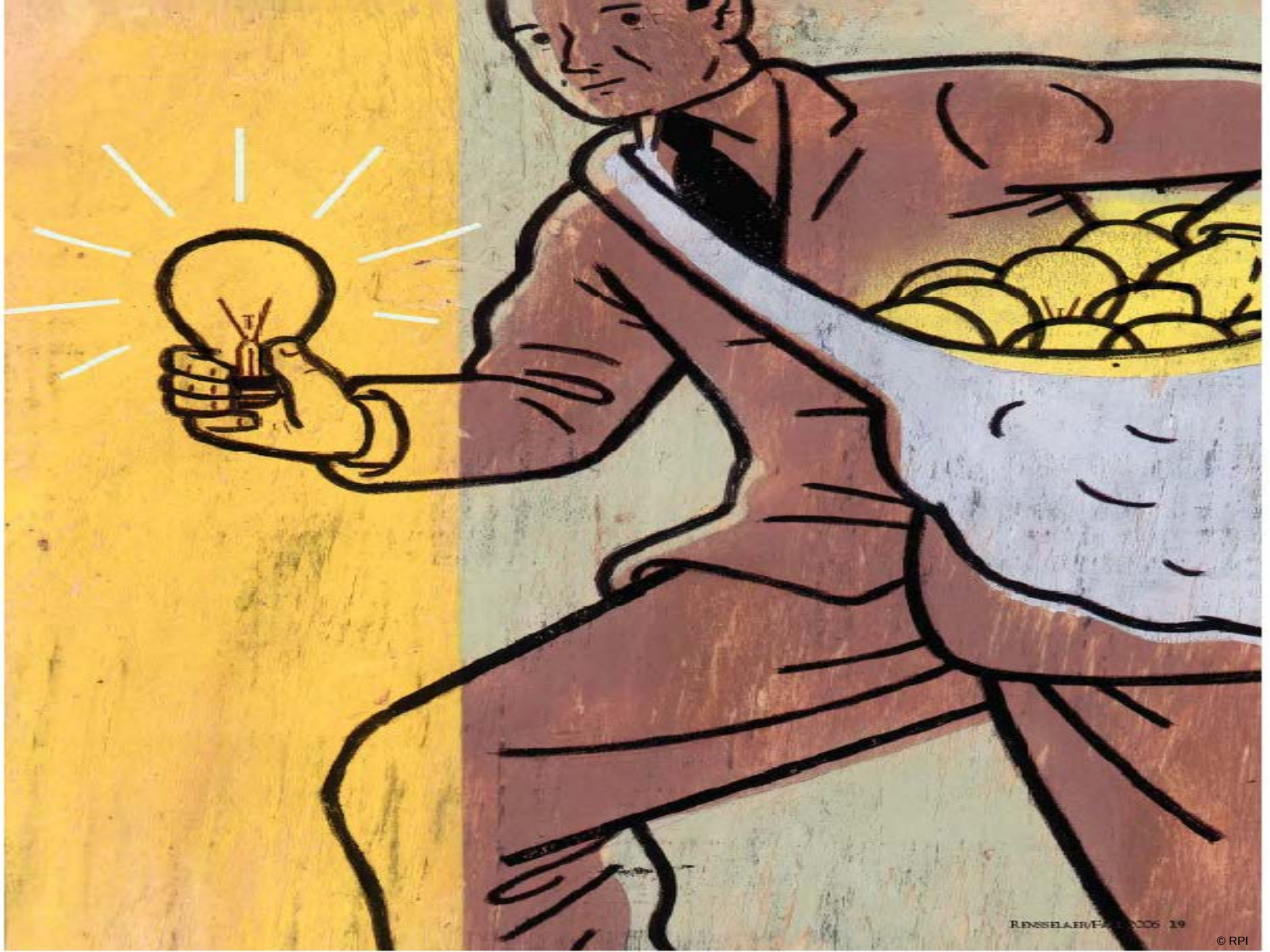
"... AND DO YOU TAKE THIS MAN, PARTS OF WHOM ARE PATENTED BY THE GENESCOPE COMPANY..."

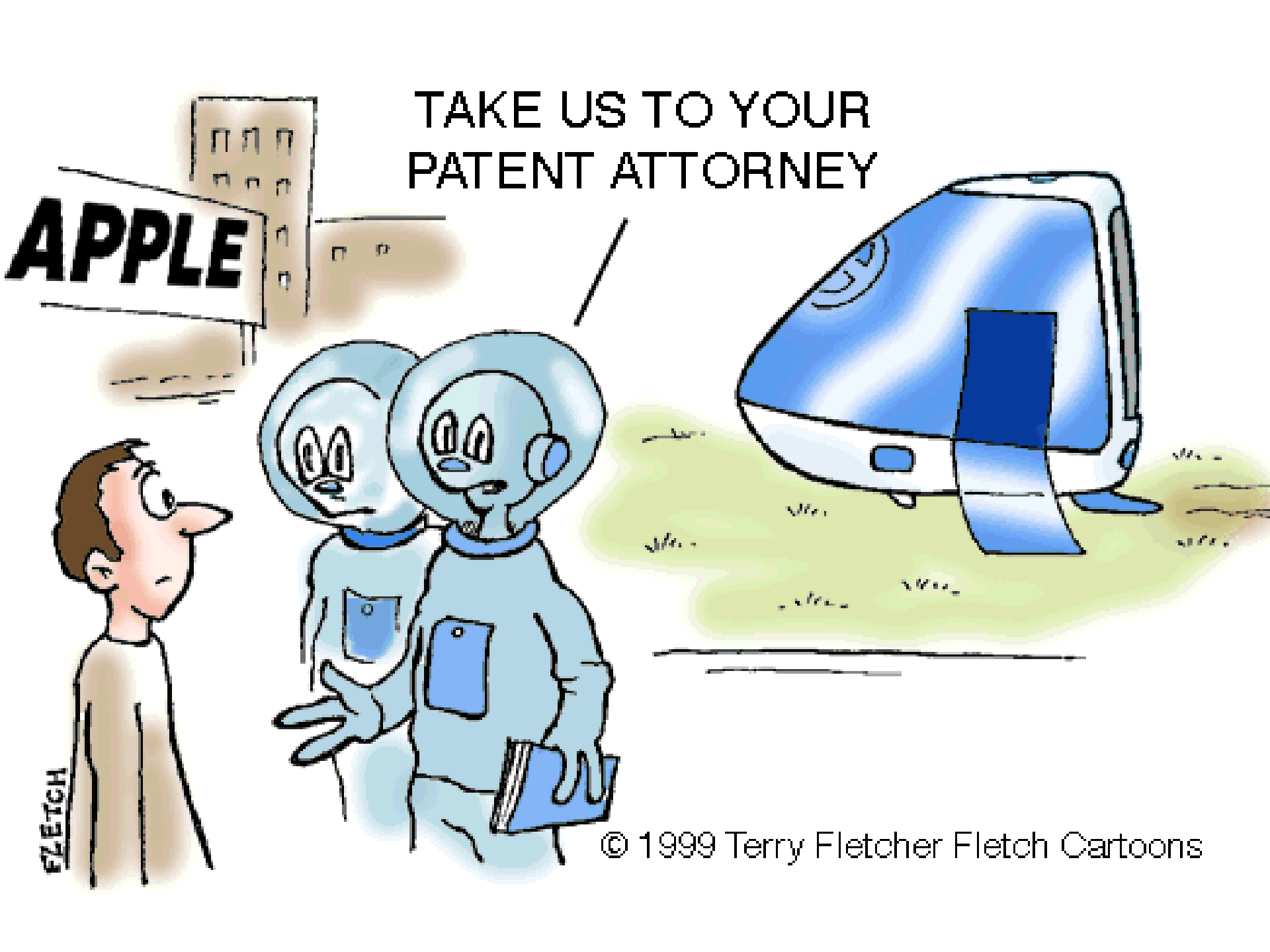
Your invention might be brilliant, but odds are somebody else thought of it (and is patenting it) too



"WHAT HAVE YOU BROUGHT?"


HERE'S MY NEW INVENTION!
OH, IT LOOKS LIKE MINE!
!!!
RENARD




TAKE US TO YOUR
PATENT ATTORNEY
APPLE
FLETCH
© 1999 Terry Fletcher Fletch Cartoons

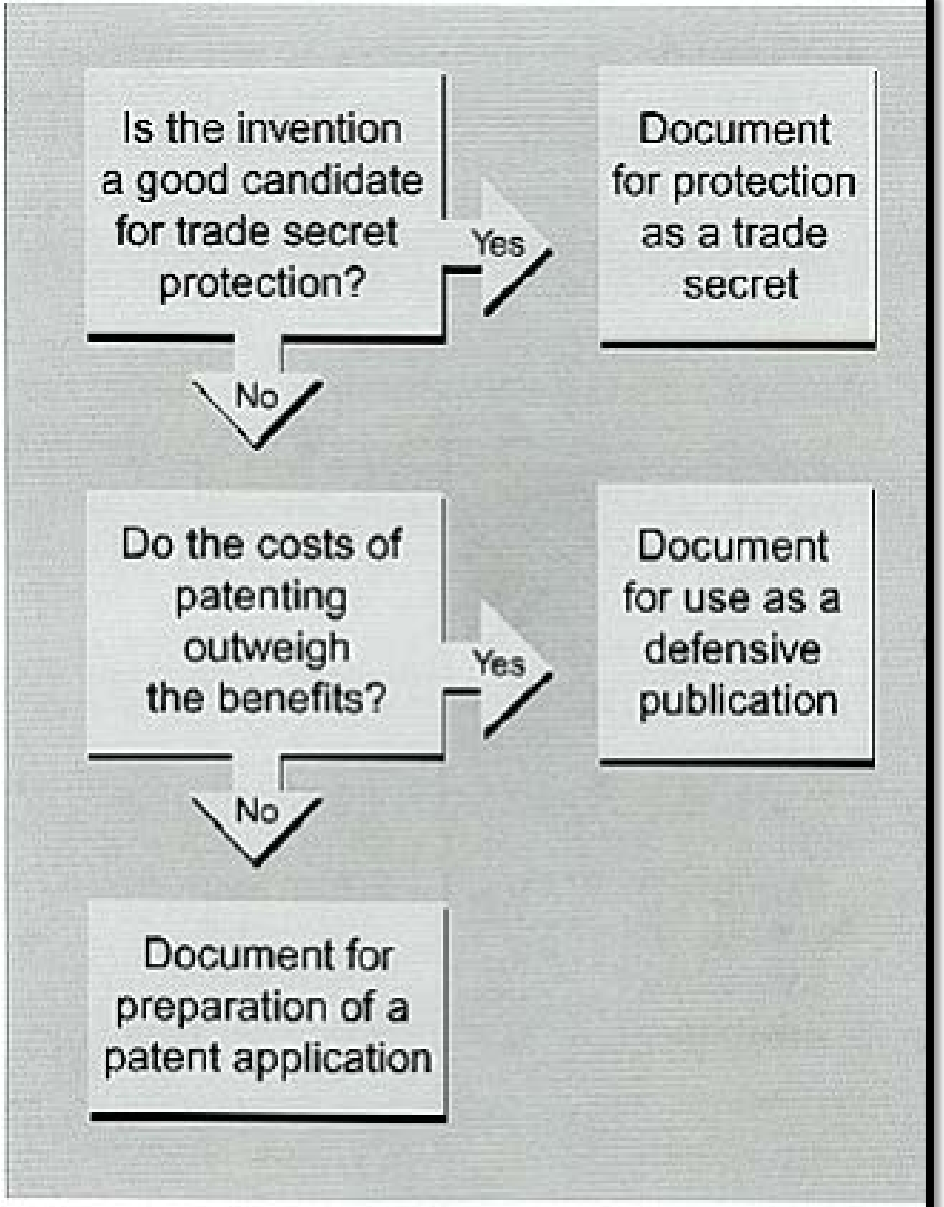
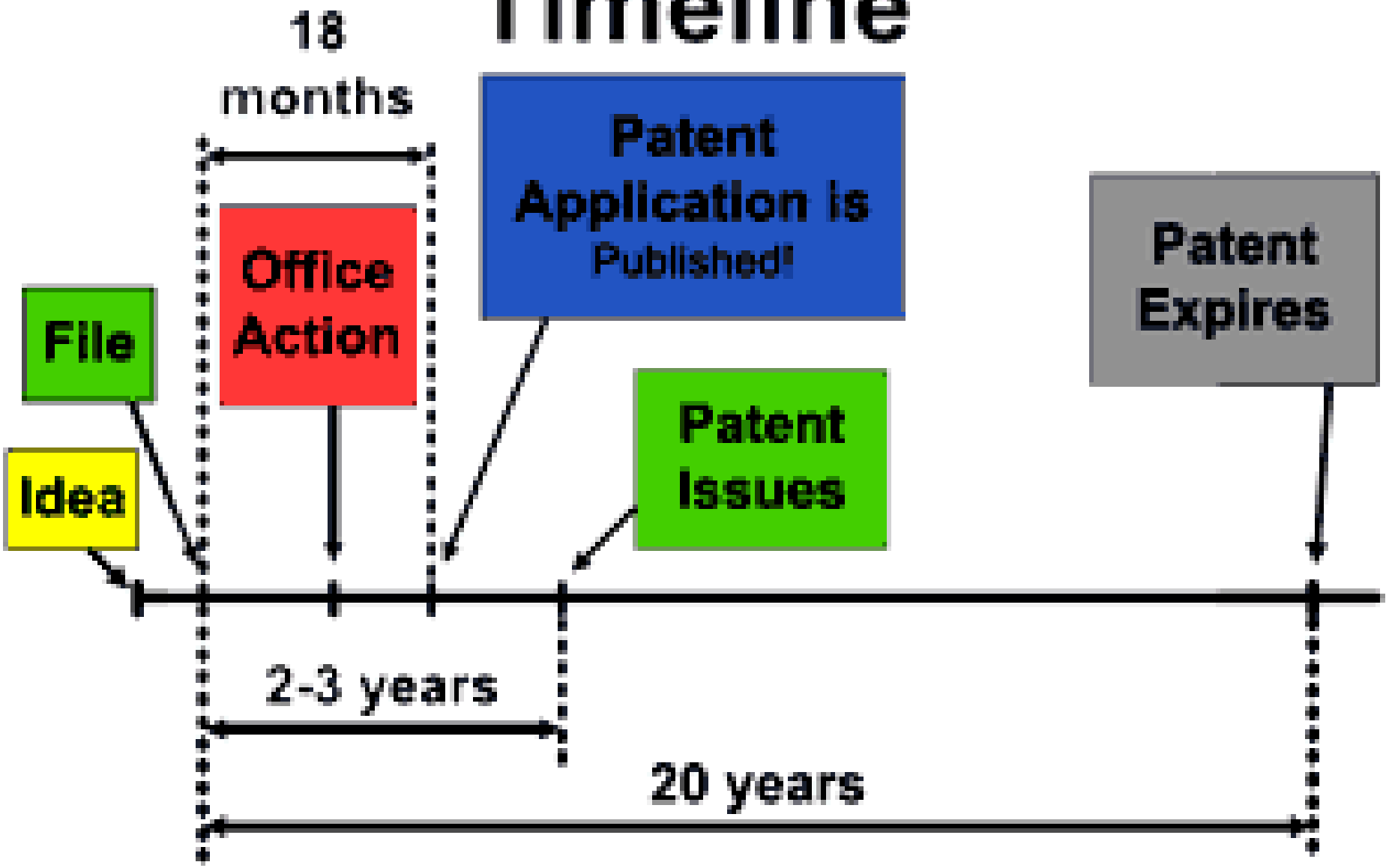


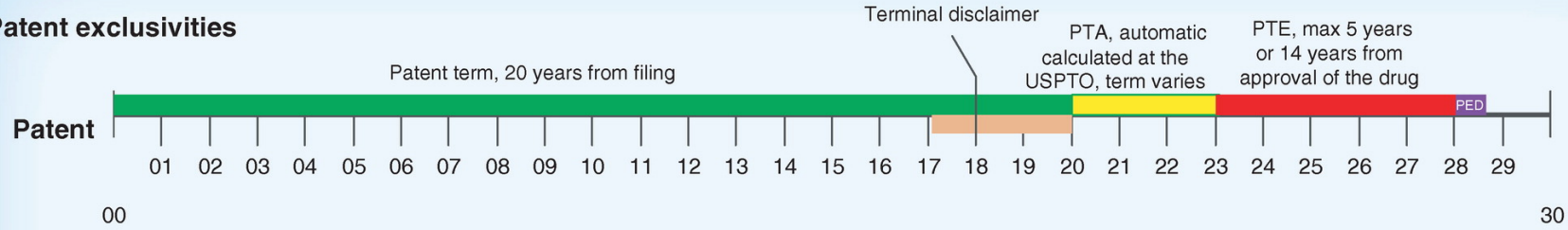
Figure 1: Flow chart showing the process for deciding whether an invention will be kept as a trade secret, patented, or made the subject of a defensive publication.

Nature Biotechnology 20, 191 - 193 (2002)

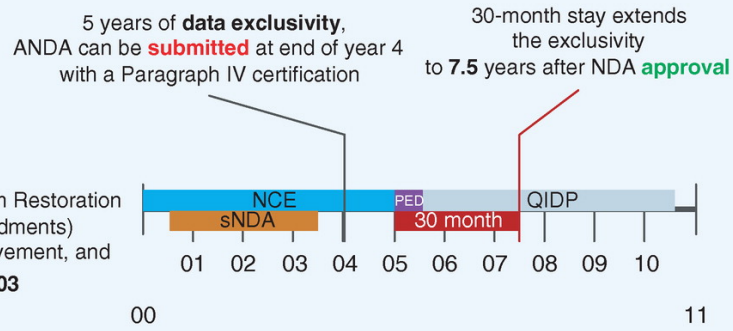
Patent Prosecution Timeline



Patent exclusivities



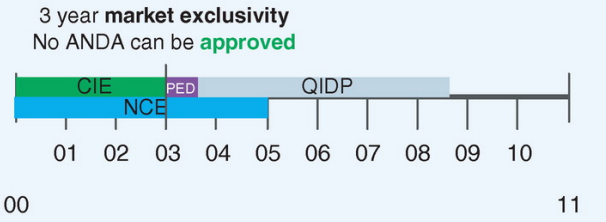
Regulatory exclusivities



NDA, 505(b)(1)

Small molecule

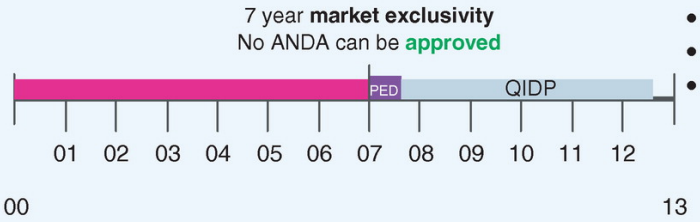
Drug Price Competition and Patent Term Restoration Act of **1984** (Hatch/Waxman Amendments) And Medicare Prescription Drug Improvement, and Modernization Act (MMA) **2003**



NDA, 505(b)(2)

Drug Price Competition and Patent Term Restoration Act of **1984**

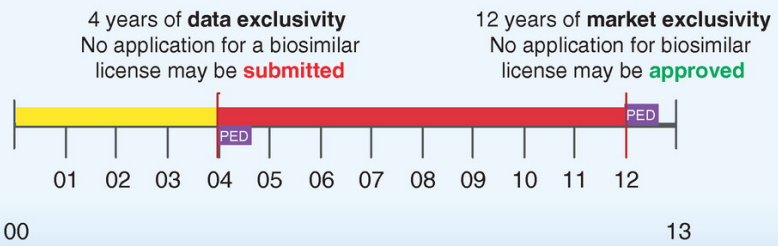
(Hatch–Waxman Amendments)



Orphan drug

Small molecule and biologics

Orphan Drug Act (ODA) of January **1983**



Biologics

Patient Protection and Affordable Care Act (PPACA), (Obamacare)

March 23, **2010**

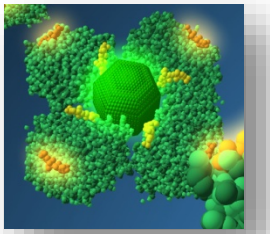
Patent exclusivities

- Patent term – 20 years
- Patent term adjustment (PTA)
- Patent term extension (PTE)
- Terminal disclaimer (TD)

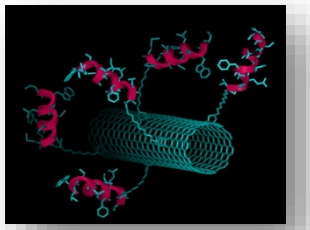
Regulatory exclusivities (data exclusivity and market exclusivity)

- New chemical entity (NCE) – 5 years (ANDA file at year 4 with paragraph IV certification)
- 30-month stay – 3 years
- Supplemental NDA
- Rx to OTC – 3 years
- Clinical investigation exclusivity (CIE) – 3 years
- Orphan drug exclusivity (ODE) – 7 years
- Pediatric exclusivity (PE) – 0.5 year
- Biologic exclusivity – 4 years and 12 years
- Generic Drug Exclusivity (GDE) – 180 days
- Qualified Infectious Disease Products (QIDP) exclusivity – 5 years

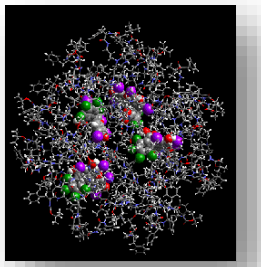
Different Terms - Same Structures



nanoparticles, nanocrystals, nanodots, colloidal crystals

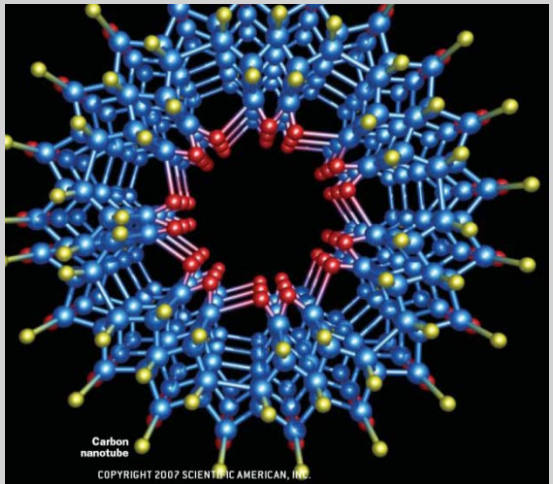


carbon nanotubes, carbon fibrils, carbon whiskers, molecular wires



dendrimers, dendritic molecules, starburst conjugates

Expert Opinion



The carbon nanotube patent landscape in nanomedicine: an Expert opinion

Drew L Harris† & Raj Bawa
†*Graves, Dougherty, Hearon & Moody, 401 Congress Avenue, Austin, Texas 78701, USA*

Carbon nanotubes (CNTs) have extraordinary properties that make them promising candidates for a wide variety of potential biomedical applications, including new therapeutics, drug delivery systems and diagnostics. Because of their enormous commercial potential across industries, a classic patent landgrab is underway as competitors are busy locking up broad patents on CNTs. This is creating a chaotic, tangled patent thicket, where the validity and enforceability of numerous patents is unclear. In this article, the authors summarize the CNT patent landscape for nanomedicine, identifying key building block patents while raising legal questions regarding their validity.

Keywords: carbon nanotubes, drug delivery, multi-walled carbon nanotubes, nanomedicine, nanotechnology, patent thickets, patents, single-walled carbon nanotubes, US Patent & Trademark Office

Expert Opin. Ther. Patents (2007) 17(9):1165-1174

Proof in the Pictures

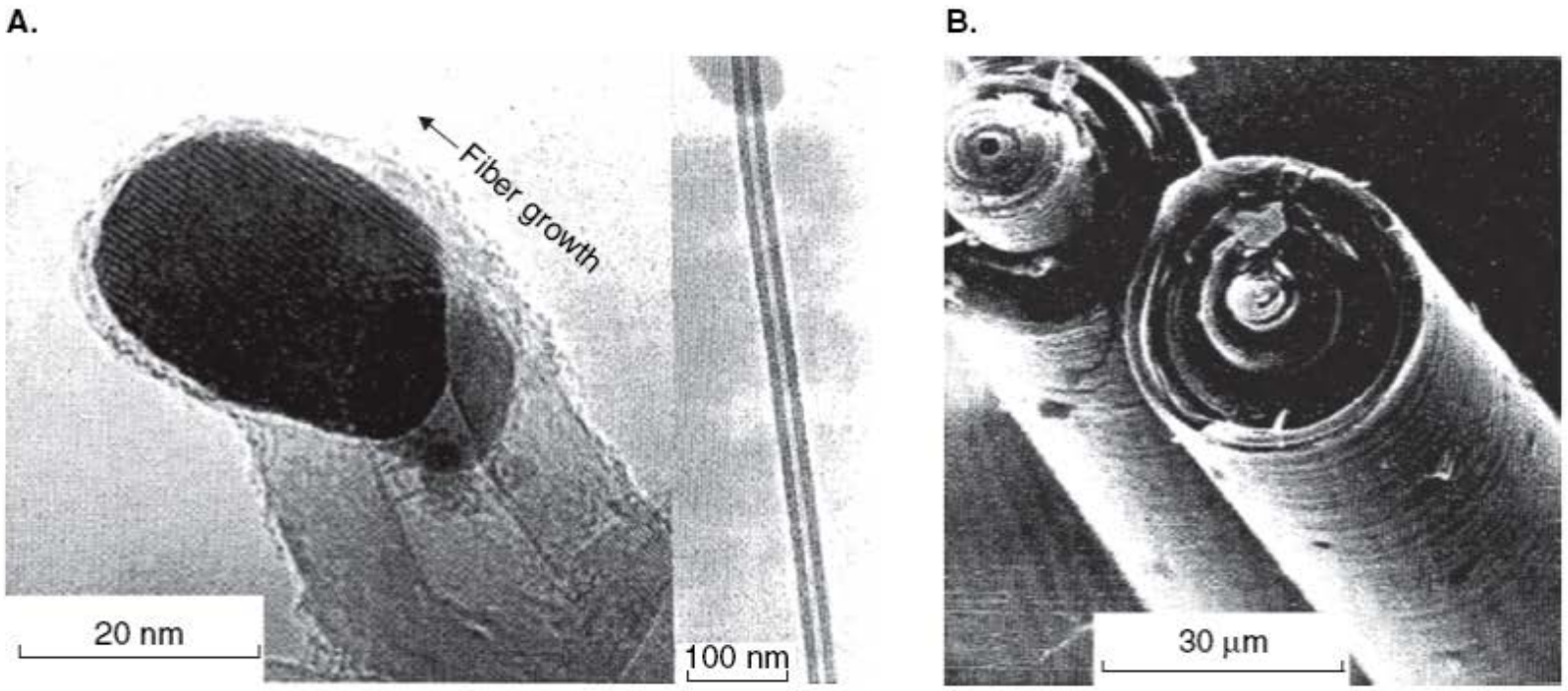
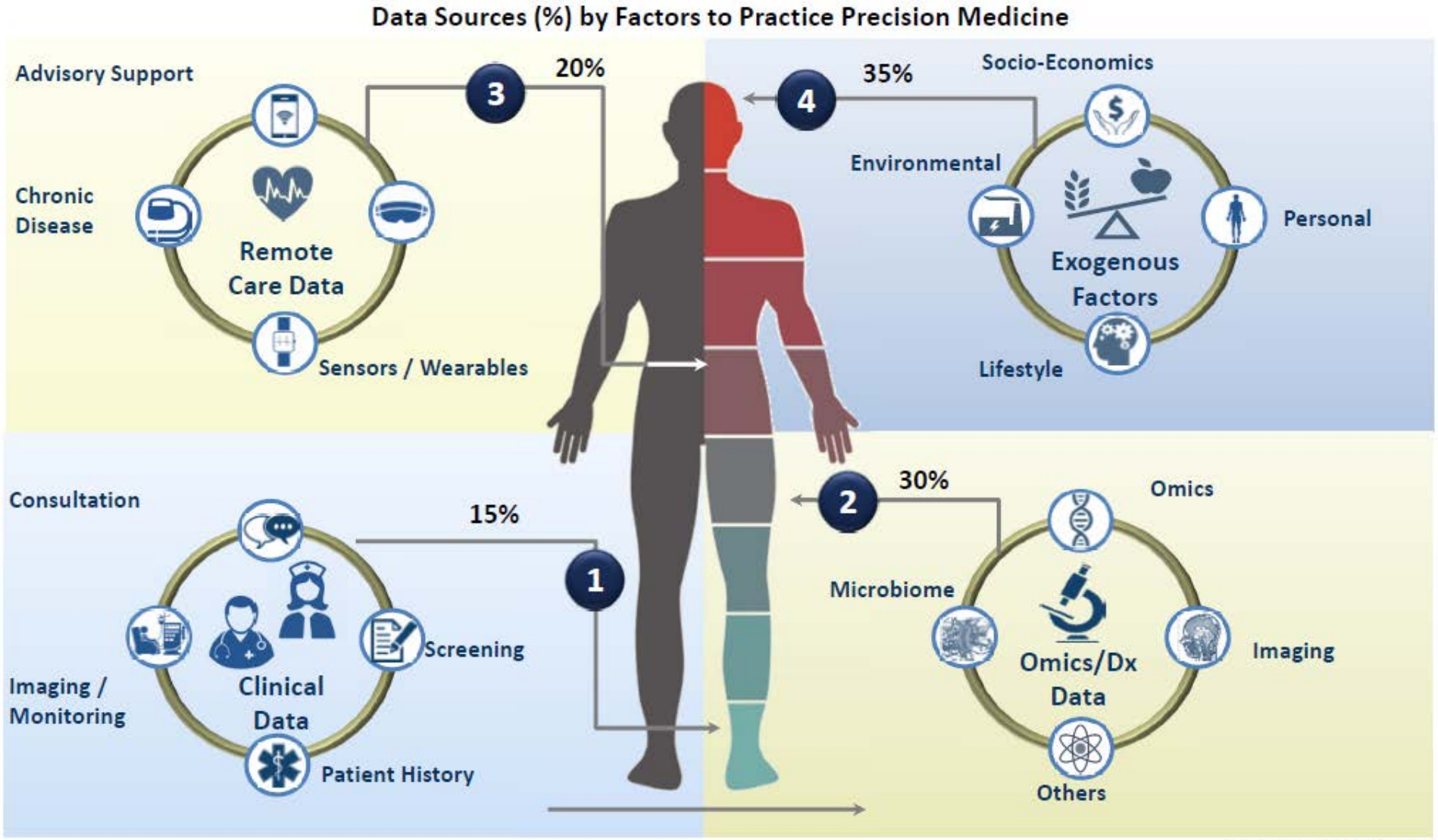


Figure 1. Images of 'vapor phase grown carbon fibers' dated 1988.

Reprinted with permission from ENDO M: Grow carbon fibers in the vapor phase: what you can make out of these strong materials and how to make them. *Chemtech* (1988) **18**(9):568-578. © Copyright (2007) American Chemical Society.

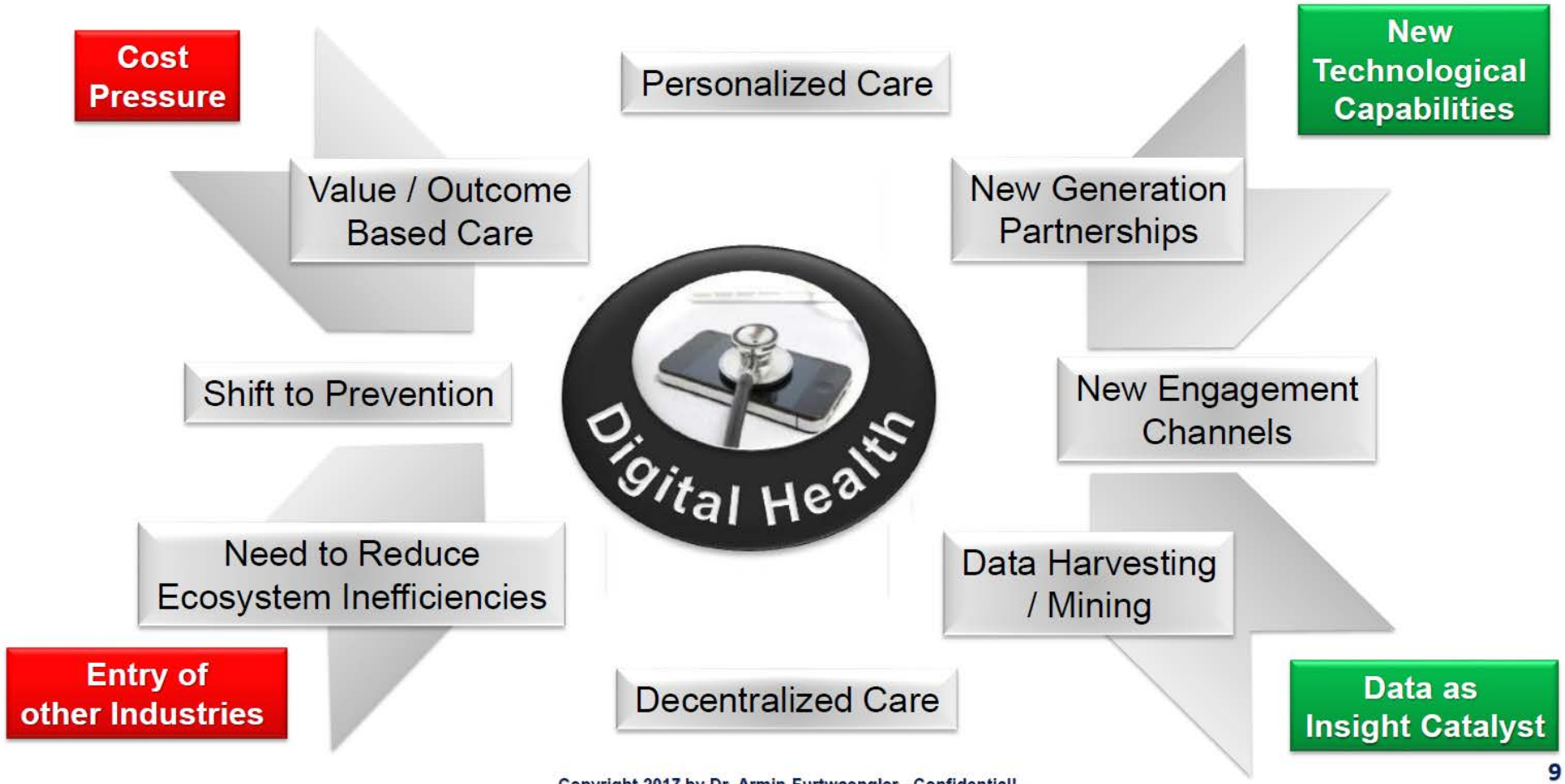
Expert Opin. Ther. Patents (2007) 17(9):1165-1174

How will Precision Medicine be Implemented?



Source: Frost & Sullivan

Burning Platform – Threats and Opportunities



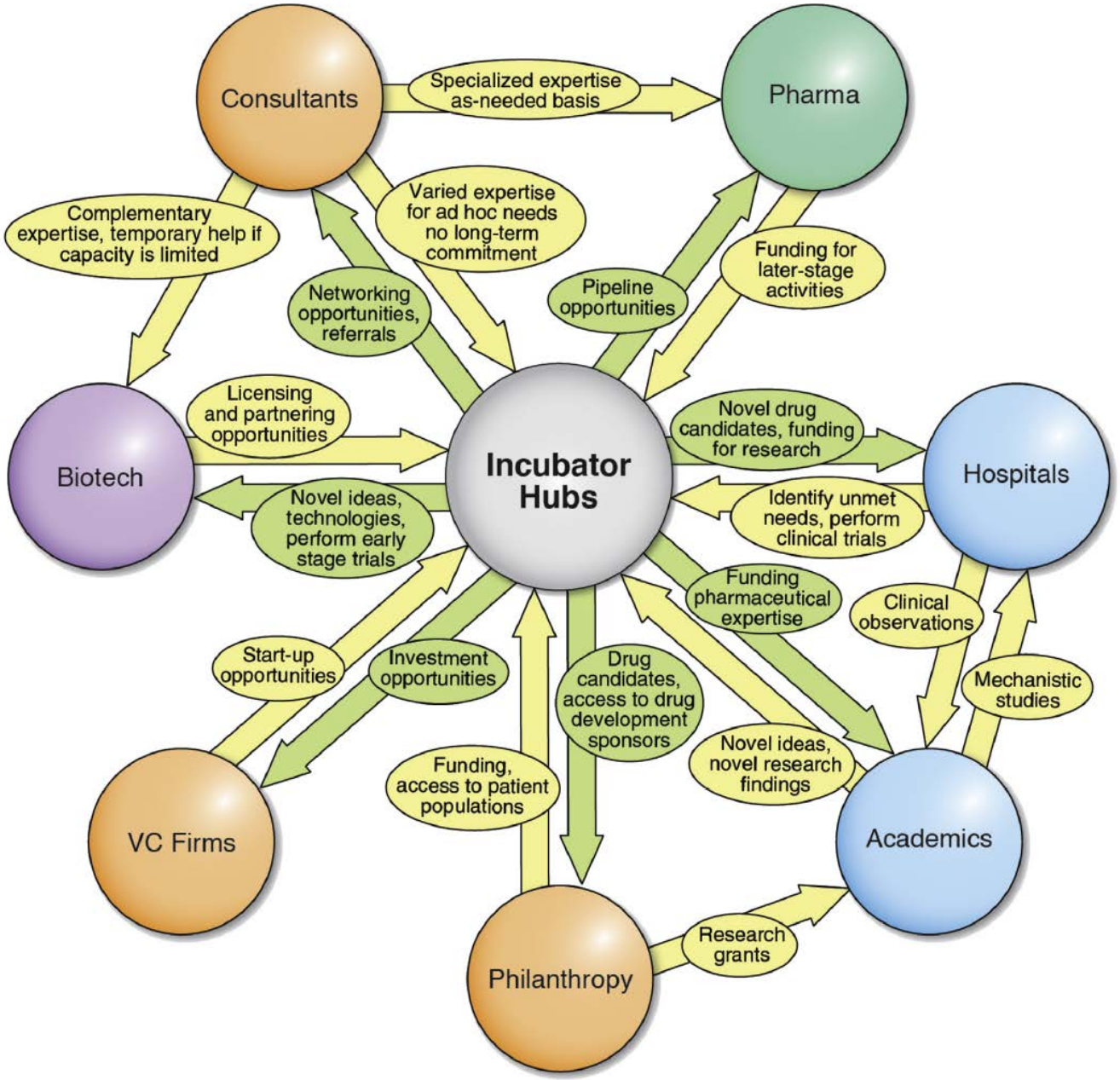
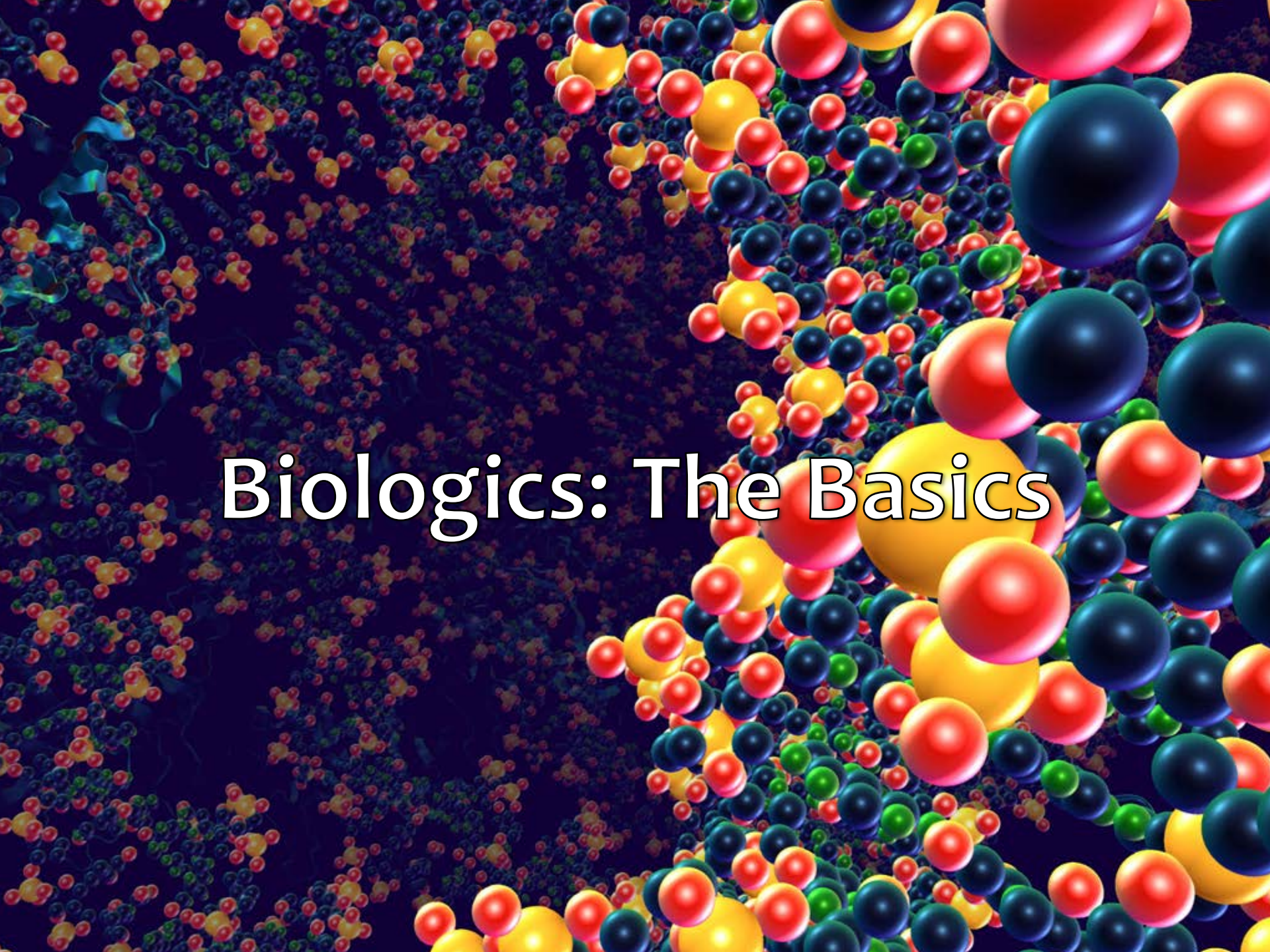
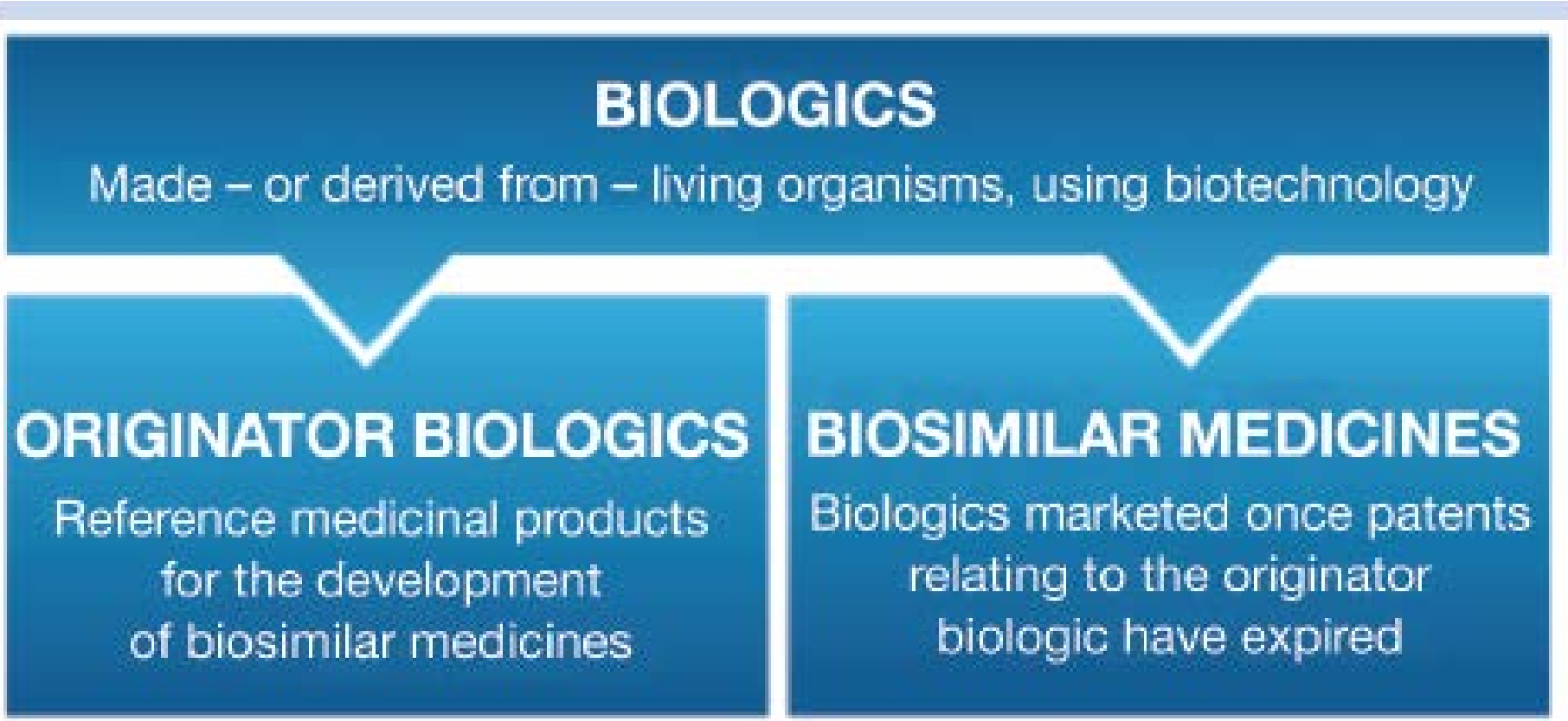


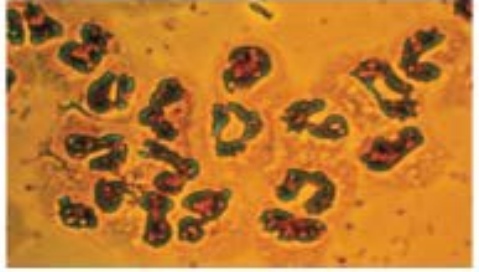
FIGURE 9.1 The integrated discovery nexus. Translational programs or centers, often based in universities or hospitals, serve as incubator hubs for helping commercialize and advance laboratory discoveries. They create a network of interactions with participants from many parts of the drug discovery ecosystem, each of which has something to gain from their involvement in the network. Examples include Stanford University's SPARK program, University of California's QB3 program, CTSI program at UCSF, and J&J's Janssen Labs (Fishburn, 2013a; Fishburn, 2014a). *(Figure is reproduced from Fishburn, 2013a with permission from Elsevier.)*

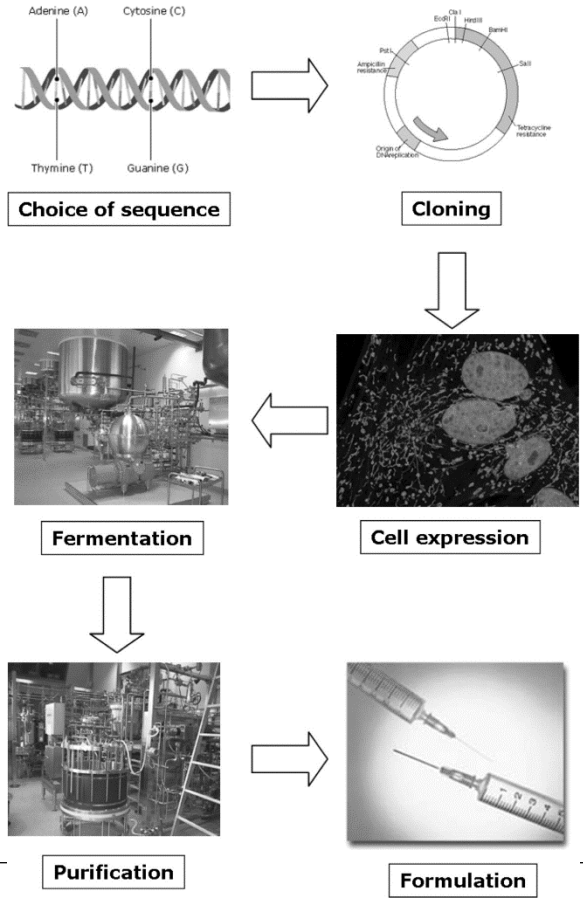

Biologics: The Basics

Biologic: originates from 'biology', the science of living organisms. Any of a class of medicines in which the active pharmaceutical ingredient comes from a living organism that cannot reasonably be synthesized by chemical means. Biosimilars are Biologics.



Used with permission from Medicines for Europe. Adapted from Biosimilars Handbook, European Generic Medicines Association, Second edition, 2011.

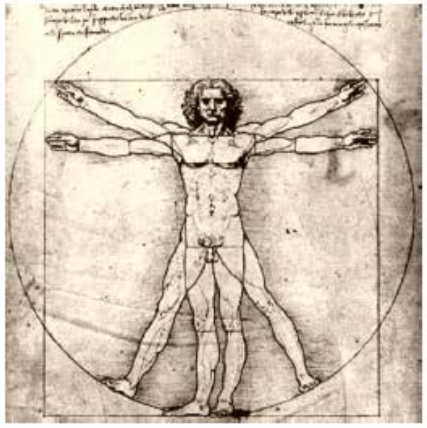


From: The protein science of biosimilars

Nephrol Dial Transplant. 2006;21(suppl_5):v4-v8. doi:10.1093/ndt/gfl474

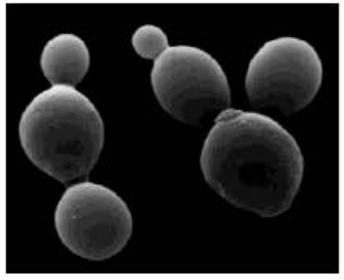
Source Materials

Mammalian cell-culture



Humans

Avian cell-culture

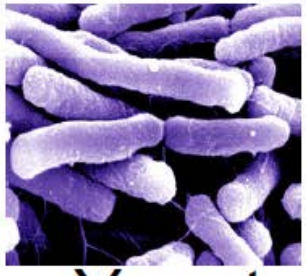


Bacteria

Mice

Transgenics

Plant cell-culture

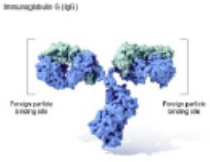


Yeast

Insect cell-culture

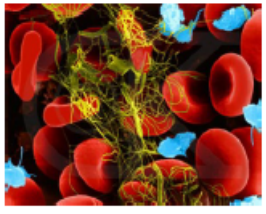
Types of Biological Products

Blood Derivatives

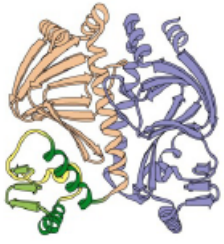


Whole Blood

Blood Components

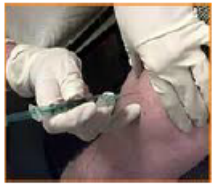


Proteins

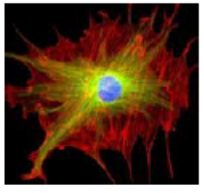


Human Tissues

Vaccines (preventive *and* therapeutic)



Allergenic Extracts



Cellular & Gene Therapies

Xenotransplantation Products

Box 2.1 Standard Nomenclature

"A nanodrug is: (1) a formulation, often colloidal, containing therapeutic particles (nanoparticles) ranging in size from 1–1,000 nm; and (2) either (a) the carrier(s) is/are the therapeutic (i.e., a conventional therapeutic agent is absent), or (b) the therapeutic is directly coupled (functionalized, solubilized, entrapped, coated, etc.) to a carrier."

Source: Bawa, R. (2016). What's in a name? Defining "nano" in the context of drug delivery. In: Bawa, R., Audette, G., Rubinstein, I., eds. *Handbook of Clinical Nanomedicine: Nanoparticles, Imaging, Therapy, and Clinical Applications*, Pan Stanford Publishing, Singapore, chapter 6, pp. 127–169.

"A biopharmaceutical is a protein or nucleic acid-based pharmaceutical substance used for therapeutic or in vivo diagnostic purposes, which is produced by means other than direct extraction from a native (non-engineered) biological source."

Source: Walsh, G. (2002). Biopharmaceuticals and biotechnology medicines: An issue of nomenclature. *Eur. J. Pharm. Sci.* **15**, 135–138.

A small-molecule drug (SMD) is a chemically synthesized pharmaceutical compound of precise structure and low molecular weight (<700 Daltons) used for therapy or in vivo diagnosis, that lacks immunogenicity in the patient but may produce off-target effects.

Source: Raj Bawa, unpublished Work, 2018.

A non-biologic complex drug (NBCD) is "[a] medicinal product, not being a biological medicine, where the active substance is not a homomolecular structure, but consists of different (closely) related and often nanoparticulate structures that cannot be isolated and fully quantitated, characterized, and/or described by physicochemical analytical means. It is also unknown which structural elements might affect the therapeutic performance. The composition, quality, and in vivo performance of NBCDs are highly dependent on the manufacturing processes of both the active ingredient and the formulation. Examples of NBCDs include liposomes, iron–carbohydrate (iron–sugar) drugs, and glatiramoids."

Source: Astier, A., Pai, A. B., Bissig, M., Crommelin, D. J. A., Flühmann, B., Hecq, J.-D., Knoeff, J., Lipp, H.-P., Morell-Baladrón, A., Mühlebach, S. (2017). How to select a nanosimilar. *Ann. N.Y. Acad. Sci.*, **1407**(1), 50–62.

Nanotechnology is "[t]he design, characterization, production, and application of structures, devices, and systems by controlled manipulation of size and shape at the nanometer scale (atomic, molecular, and macromolecular scale) that produces structures, devices, and systems with at least one novel/superior characteristic or property."

Source: Bawa, R. (2007). Patents and nanomedicine. *Nanomedicine* (*London*), **2**(3), 351–374.

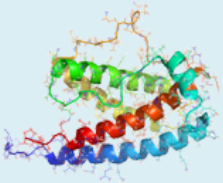
INCREASING level of complexity →

Small-chemical molecule[2-4]

For example:
Salicylic acid

- Chemically synthesized
- Well-defined structure
- Low molecular weight

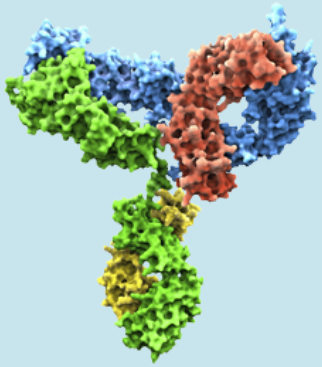
Biologic molecule[2,4,5]



For example:
Filgrastim

- Derived from living material
- Larger, more complex structure
- High molecular weight

Complex biologic[4,6,7]



For example:
Monoclonal antibody

- Derived from living material
- Most complex structure
- Very high molecular weight

Note: Illustrations are not to scale.

Differences Between Small-Molecule Drugs and Biologics

Characteristics	Small-Molecule Drugs	Biologics
Product	Chemical-based	Protein-based
Size	Small	Large
Molecular structure	Simple	Complex
Heterogeneity	Single entity	Heterogeneous mixture
Can be fully characterized	Yes	No
Relative sensitivity to storage and handling	Stable	Sensitive
Potential for immune reactions	Lower	Higher

Table 1.1 Properties of biologics versus small-molecule drugs

Property	Biologics	Small-Molecule Drugs
Size and MW	generally large and high MW; MW >700 Da; complex structure	generally small and low; MW <700 Da; simple and defined structure
Manufacturing	numerous critical process steps; highly susceptible to slight alterations in production process; lengthy and complex purification; great possibility of contamination and detection/removal often impossible	fewer critical process steps; not affected by slight alterations in production process; easy to purify; contamination can generally be avoided and detection/removal easy
Composition	protein-based; amino acids; heterogenous mixture that may include variants; may involve post-translational modifications	chemical-based; synthetic organic compound(s); homogenous drug substance (single entity)
Origin	isolated from living cells or recombinantly produced	chemical synthesis
Toxicity	more consistent with exaggerated pharmacology than off-target toxicity; much greater contact surface area for binding allows access to a much wider range of protein targets as well as a more specific binding interaction, decreasing the potential for off-target effects	drug product or metabolites that are generated can be toxic; target binding results in the small-molecule drug being nearly completely buried within a hydrophobic pocket of the protein target to maximize hydrophobic contact plus create a more stable complex, thereby effectively limiting targets to those that possess solvent accessible pockets

Property	Biologics	Small-Molecule Drugs
Dosing Frequency	increased blood circulation time can allow far less frequent dosing	greater dosing frequency
Half-Life	variable; longer half-life (hours, days, weeks)	variable; mostly shorter half-life (hours to days)
Clearance	slow	rapid
Pharmacokinetic (PK) and Distribution	target can affect PK behavior (TMDD); larger molecule(s) and hence reach blood via lymphatics; subject to proteolysis during interstitial and lymphatic transit; distribution generally limited to plasma and/or extracellular fluid	mostly linear PK; nonlinearity from saturation of metabolic pathways; rapid entry into systemic circulation via capillaries; distributed to any combination of organ/tissue
Cost	high, often extremely high	generally low
Drug–Drug Interaction (DDI)	rare or few examples, mostly pharmacodynamic (PD)-related	possible and many examples; metabolic and/or PD related
Off-target Action	rare; mostly "on-target" effects	often "off-target" effects
Mode of Action	regulatory or enzyme activity to replace/augment cell action; may target cell surface to induce action; binding to cell-surface receptors and other markers specifically associated with or overexpressed; limited to extracellular and cell surface interactions	antagonistic/agonistic activity on intracellular and extracellular targets
Storage and Handling Risk	variable; sensitive to environmental conditions (heat and shear)	relatively stable

Property	Biologics	Small-Molecule Drugs
Contamination Risk	high	low
Structure	may or may not be precisely elucidated or known; inherent variability due to complex manufacturing	precisely defined structure (or structures, e.g., racemic mixtures)
Delivery	generally parenteral (e.g., IV and SC)	various routes; generally oral
Dispensed By	physicians (often specialists) or hospitals	general practitioner or retail pharmacies
Duration of Action	long; days to weeks	short; hours
Characterization	less easily characterized; cannot always be fully characterized	can be fully characterized
Immunogenicity	low to high; usually antigenic and hence potential exists	often non-antigenic and hence low to none
Toxicity	receptor-mediated toxicity	specific toxicity
FDA Approval	licensed under the provisions of both the FD&C Act and the PHS Act (for exceptions see Box 1.1); biologics approved by the FDA are referred to as New Biological Entities (NBEs); a new drug application for an NBE is called a Biologic License Application (BLA) (see Fig. 1.1a)	licensed under the FD&C Act; small-molecule drugs approved by the FDA are known as New Molecular Entities (NMEs); a new drug application for an NCE is known as a New Drug Application (NDA) (see Fig. 1.1a)

Property	Biologics	Small-Molecule Drugs
Compilation	*Purple Book* published by the FDA lists biologics, their biosimilars and interchangeable generic equivalents	*Orange Book* published by the FDA lists drugs and their generic equivalents
Follow-on Versions	biosimilars (see Section 1.6); high barriers to entry; follow-ons will not be identical to the reference innovator product; preclinical and clinical (i.e., safety/efficacy) studies are needed to demonstrate comparability	generics (see Section 1.6); preclinical analytical methods can be used to validate and demonstrate comparability; full clinical studies not needed; follow-ons have identical API(s), strength, dosage form, route, and purity
Patent Issues	patent prosecution and litigation are often more complex; patents and legal exclusivities may delay the FDA approval of applications for biosimilars	patent prosecution and litigation generally less complex; patents and legal exclusivities may delay the FDA approval of applications for generics
Selectivity	high species selectivity (affinity/potency)	generally low species selectivity
Targets	multiple target binding	mostly a single or few targets

Abbreviations: BLA, Biologic License Application; Da, Daltons; DDI, drug–drug interaction; FD&C Act, Federal Food, Drug, and Cosmetic Act; IV, intravenous; MW, molecular weight; NBE, New Biological Entity; NME, New Molecular Entity; NDA, New Drug Application; TMDD, target mediated drug disposition; PD, pharmacodynamic; PHS Act, Public Health Service Act; PK, pharmacokinetic; SC, subcutaneous; API, active pharmaceutical ingredient.

European Medicines Agency - A biosimilar is a biological medicine that is developed to be similar to an existing biological medicine (the 'reference medicine'). When approved, a biosimilar's variability and any differences between it and its reference medicine will have been shown not to affect safety or effectiveness.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

United States Food and Drug Administration - A biosimilar is a biological product that is highly similar to a US licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency of the product.

FDA U.S. FOOD & DRUG ADMINISTRATION

World Health Organization - A biosimilar is a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product.

World Health Organization

Nano: The Big Picture

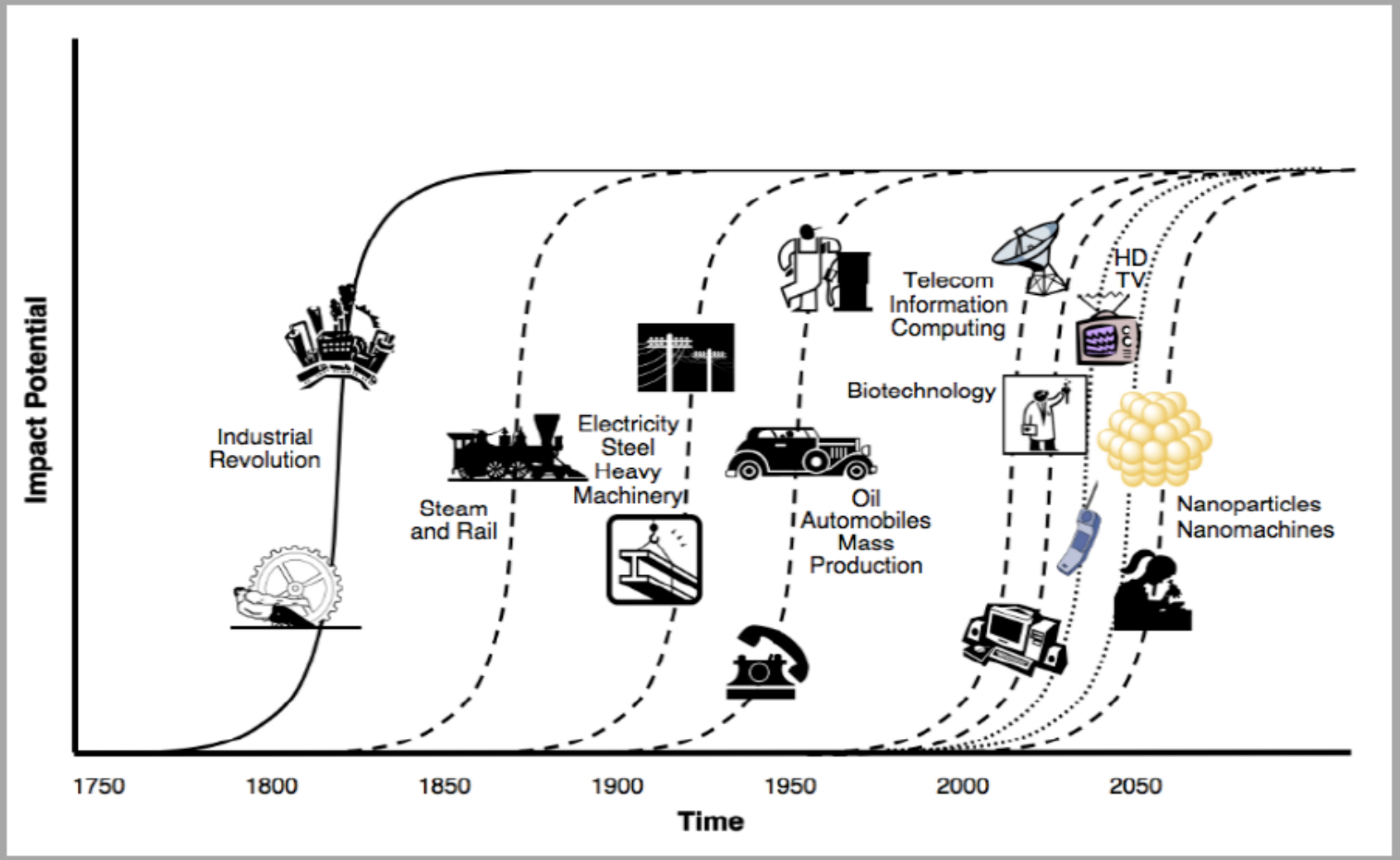
Terms with the prefix “nano”

Nano term
Nanotechnology
Nanoscale
Nanometre/nanometer
Nanotube
Nanoparticle
Nanoscience
Nanostructure
Nanomaterials
Nanofabrication
Nanoelectronics
Nanosystems
Nanobiotechnology
Nanodevices
Nanolithography
Nanoengineering
Nanofluidics

nanoscience
nanobiology
nanochemistry
nanophysics
nanobiotechnology
nanoelectronics
nanobiomimetrics
nanomanufacturing
nanolithography
nanooptics
nanoengineering
nanotribology
nanomicroscopy
nanotechnology
nanomaterials
nanomedicine
nanoceramics
nanophotonics
nanofabrication
nanometrology
nanofluidics
nanogeology
nanolithography
nanoelectromechanics

Another Industrial Revolution?

There have been many technological revolutions. Is nano the next one?



The scale of things

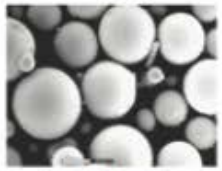
Things natural

Dust mite

200 μm

Ant

~5 mm

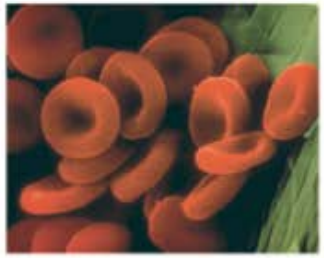


Fly ash

~10–20 μm

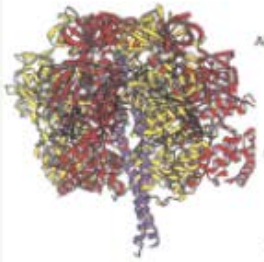
Human hair

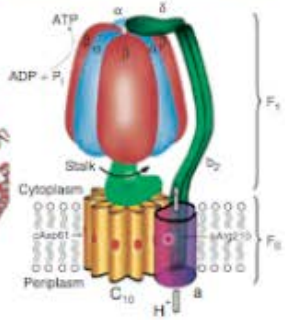
~60–120 μm



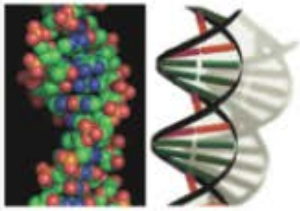
Red blood cells

~7–8 μm





ATP synthase

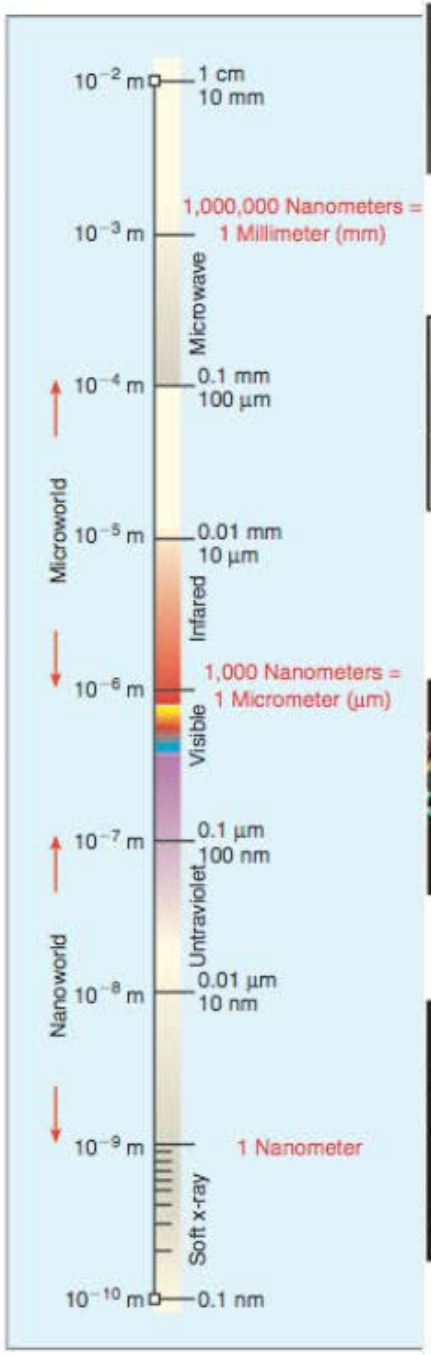


DNA

~2–1/2 nm diameter

Atoms of silicon

spacing 0.078 nm

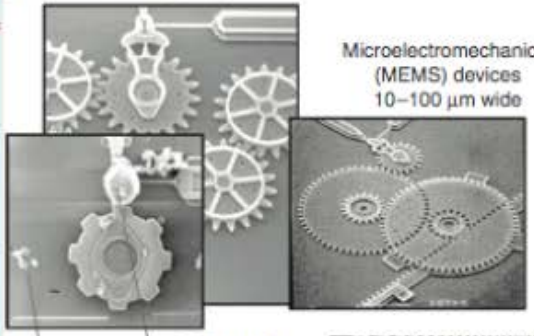


The scale of things

Things manmade

Head of a pin

~1–2 mm



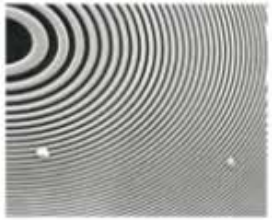
Microelectromechanical

(MEMS) devices

10–100 μm wide

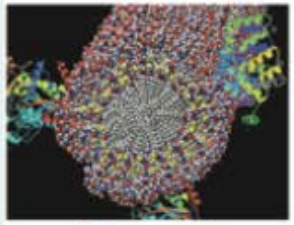
Pollen grain

Red blood cells



Zone plate x-ray "Lens"

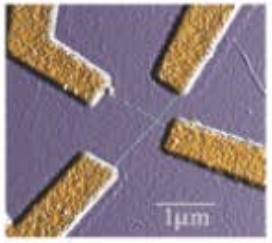
outer ring spacing ~35 nm



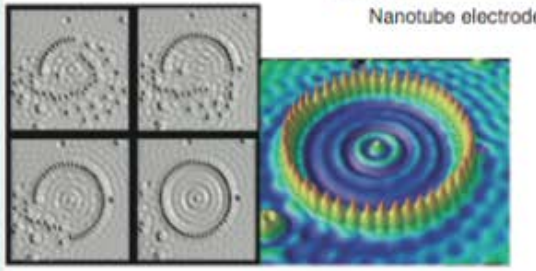
Self-assembled,

nature-inspired structure

many 10s of nm



Nanotube electrode

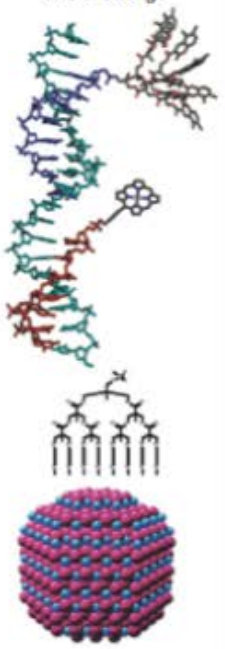


Quantum corral of 48 iron atoms on copper surface

positioned one at a time with an STM tip.

Corral diameter is 14 nm

The challenge



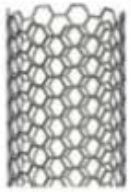
Fabricate and combine nanoscale building blocks to make useful devices, e.g., a photosynthetic reaction center with integral semiconductor storage

Carbon

buckyball

~1 nm

diameter



Carbon nanotube

~1.3 nm diameter

Courtesy of the

Office of Basic Energy Sciences

Office of Science, U.S. DOE

By the way....

The prefix "nano" in the SI measurement system denotes 10^{-9} or one-billionth. There is not even a consensus over whether the prefix "nano" is Greek or Latin. While the term "nano" is often linked to the Greek word for "dwarf," the ancient Greek word for "dwarf" is actually spelled "nanno" (with a double "n") while the Latin word for dwarf is "nanus" (with a single "n").

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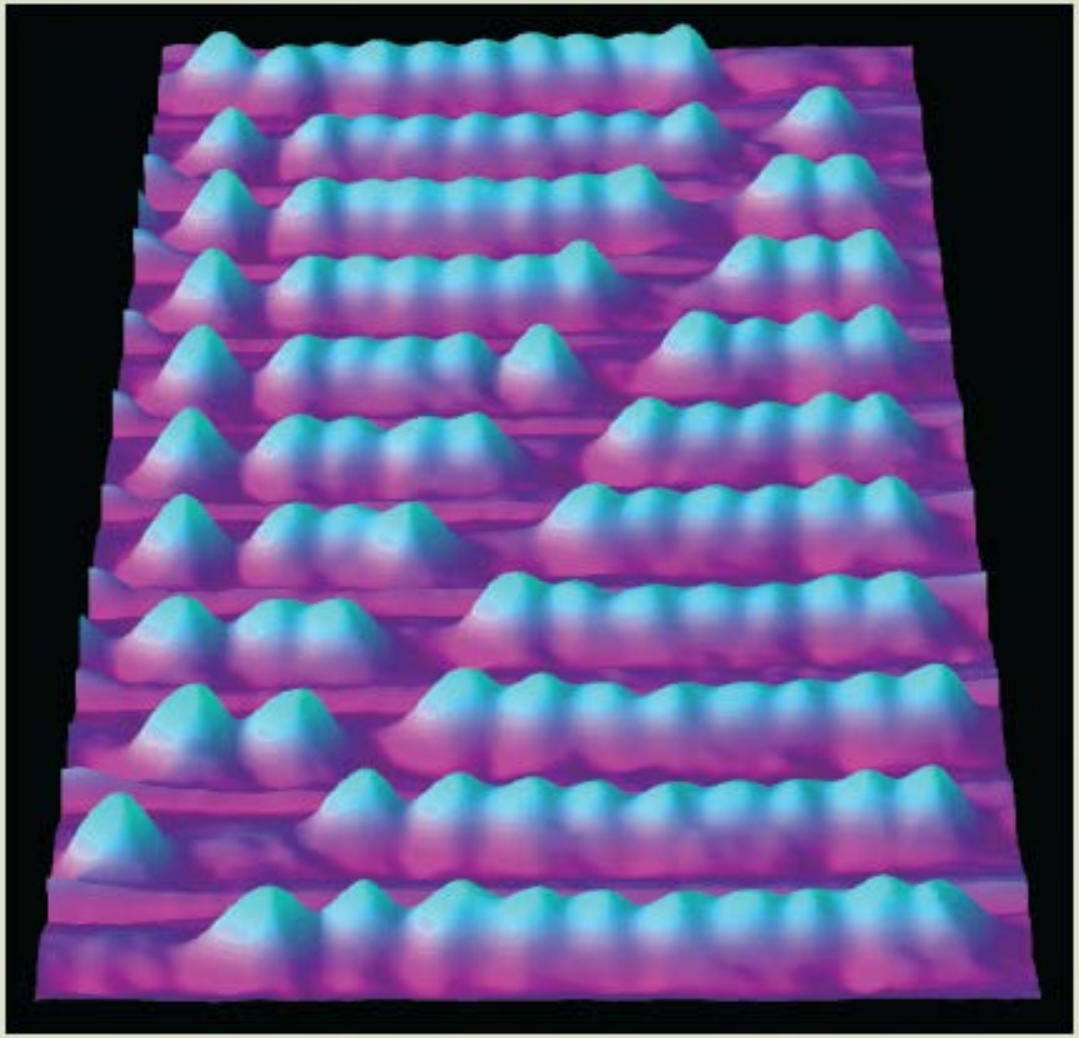
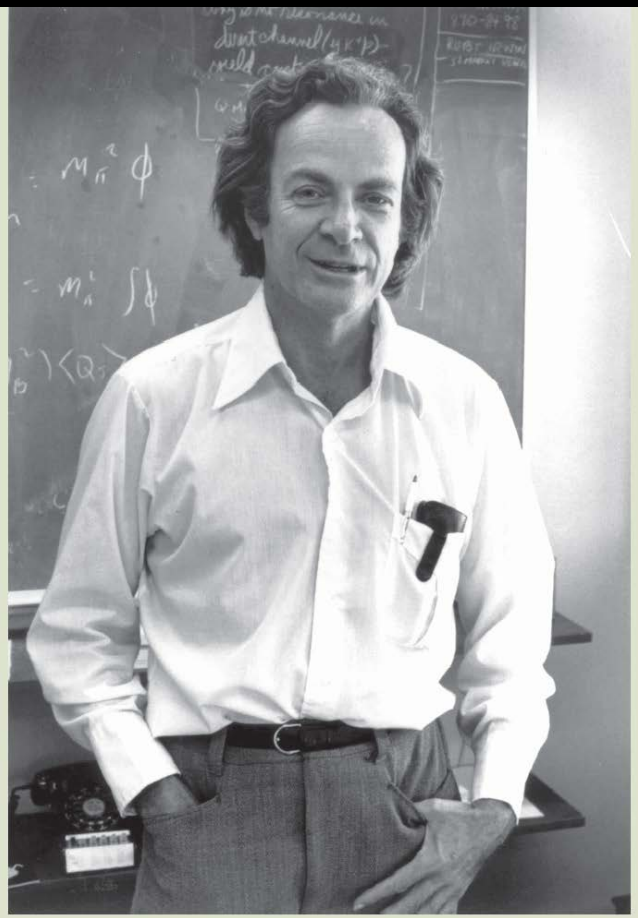
27

A nanoscale abacus created in the IBM-Zurich laboratory by Cuberes et al. The beads are actually C_{60} molecules. The rails along which the beads are moved are steps in the copper substrate. Manipulation (calculation) is accomplished with the tip of an STM.



Courtesy of IBM Zurich Research Laboratory. With permission.

There's Plenty of Room at the Bottom

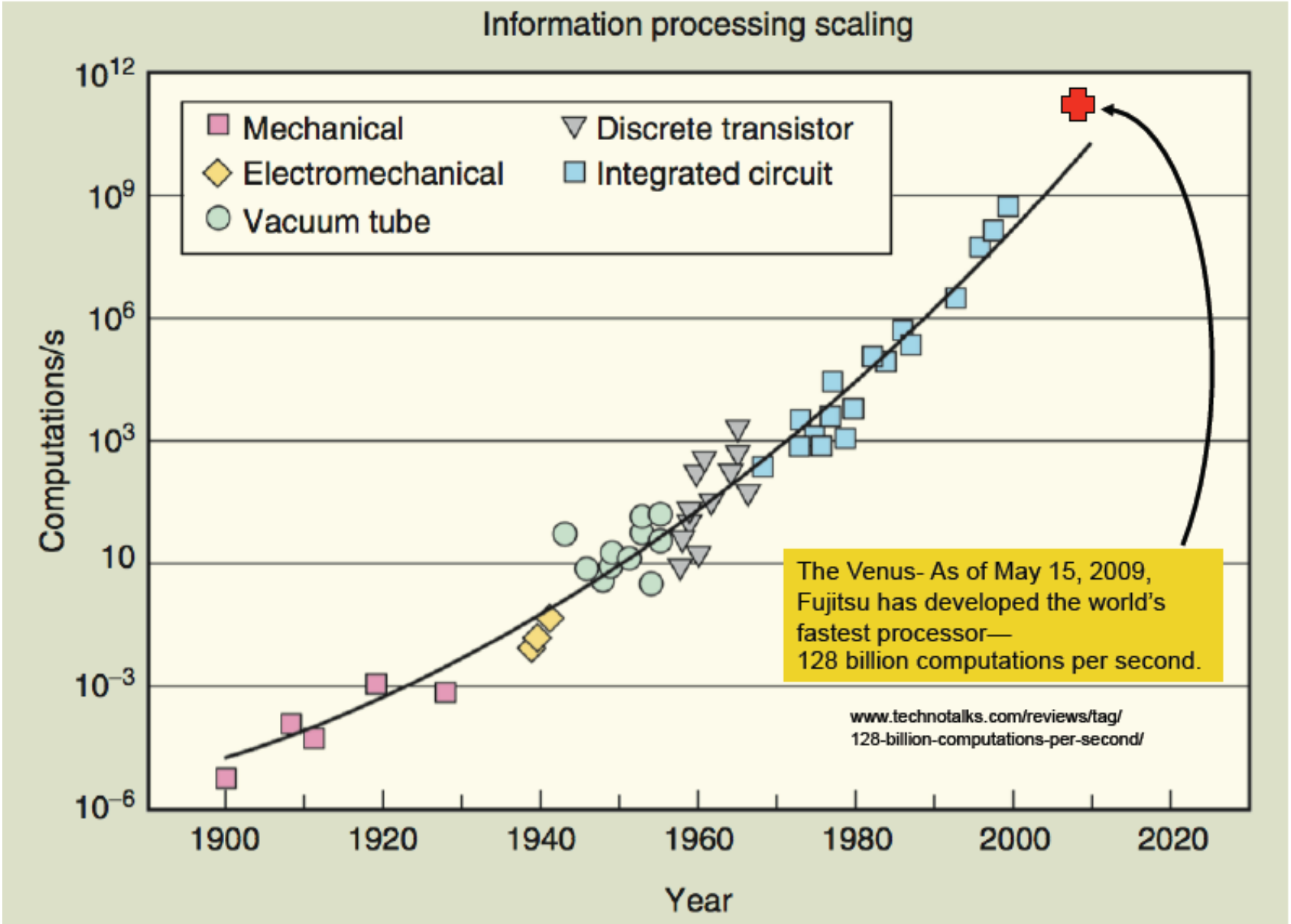


Source: Photograph of Richard Feynman used by permission of Melanie Jackson Agency, LLC. and Caltech Public Relations.

I would like to describe a field, in which little has been done, but in which an enormous amount can be done in principle. … What I want to talk about is the problem of manipulating and controlling things on a small scale.

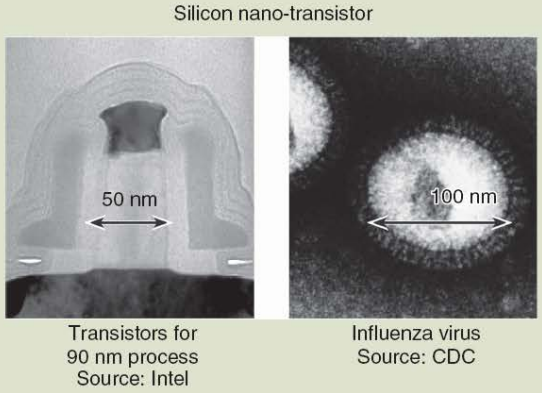
Noblest Richard Feynman, Caltech, 1959

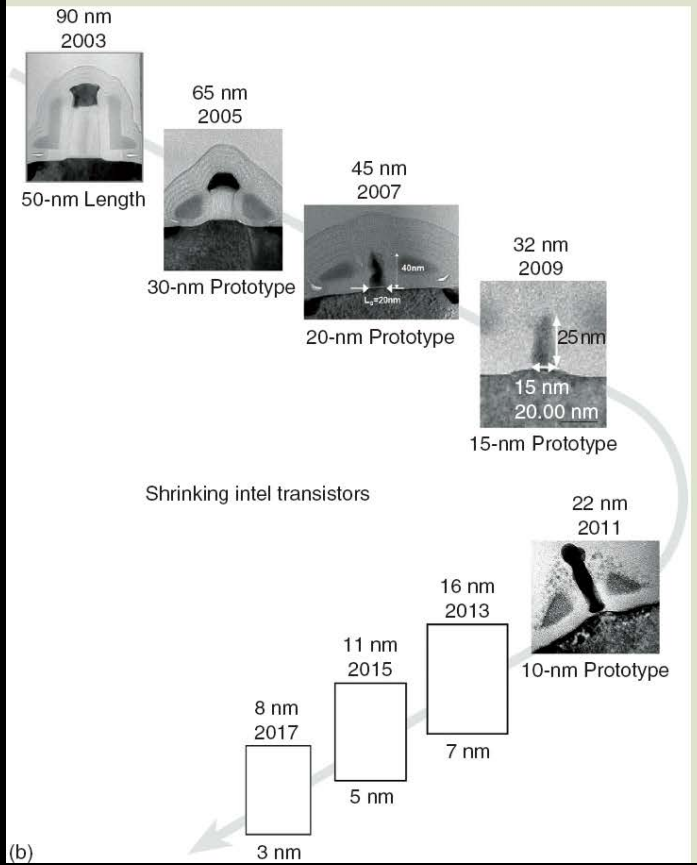
An adaptation of Moore's law shows how computing power has increased since the onset of the first mechanical computing devices.



Source: Image courtesy of the IBM Corporation

(a) A vintage 2003 transistor fabricated by the Intel Corporation is compared to the human influenza virus. We are now able to make devices smaller than one of the smallest "complete" biological structures. (b) The decreasing trend in transistor size is shown. By 2017, transistors under 10 nm in size are expected to be components in chips.

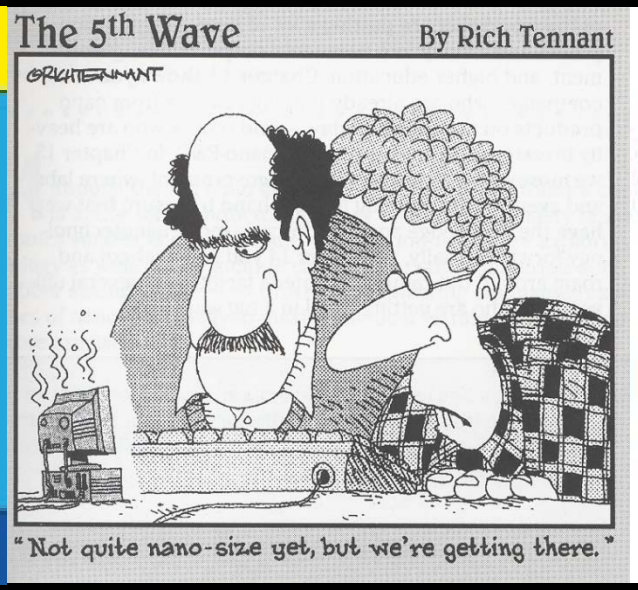


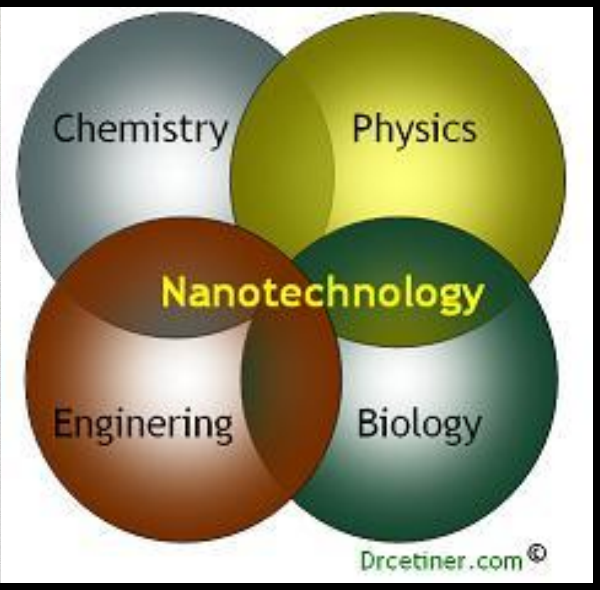


What is Nanotechnology?

The design, characterization, production, and application of structures, devices, and systems by controlled manipulation of size and shape at the nanometer scale (atomic, molecular, and macromolecular scale) that produces structures, devices, and systems with at least one novel/superior characteristic or property.

-R. Bawa . *Nanomedicine* 2(3):351-374 (2007)

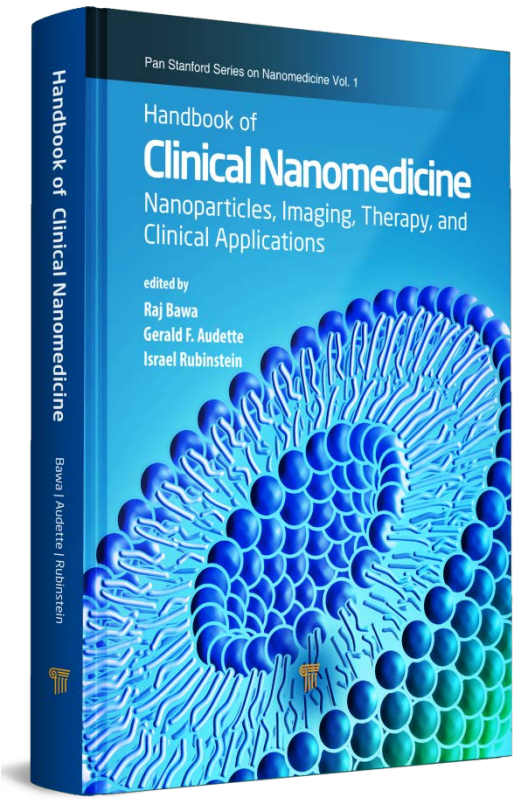




What's in a Name? Defining "Nano" in the Context of Drug Delivery[1]

Raj Bawa, MS, PhD

Patent Law Department, Bawa Biotech LLC, Ashburn, Virginia, USA
Department of Biological Sciences, Rensselaer Polytechnic Institute, Troy, New York, USA
American Society for Nanomedicine, Ashburn, Virginia, USA



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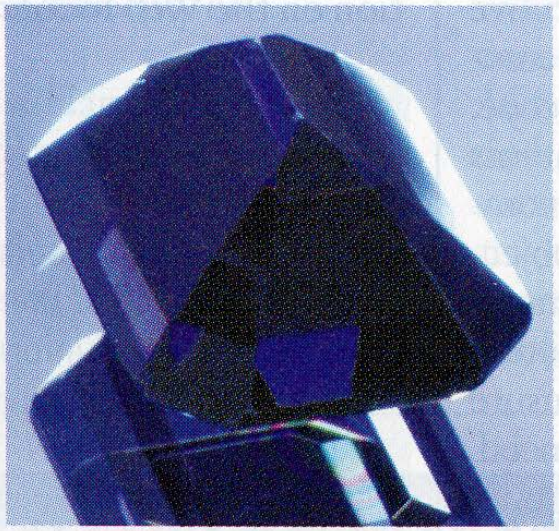


COURTESY OF JOCHEN MANNHART

VACANCY BLUES Ripping a few oxygen atoms out of $SrTiO_3$'s crystalline lattice transforms the diamond-like insulator into a deep blue conductive crystal.

.22

Thirty-five xenon atoms on a nickel (110) surface at ultralow temperature were placed to spell "IBM" with the aid of an STM by Donald Eigler and his group at the IBM Almaden Research Center. The actual writing took 22 hours to complete. The image was published in Time Magazine *in 1990 and formally ushered in the* Nano Age.

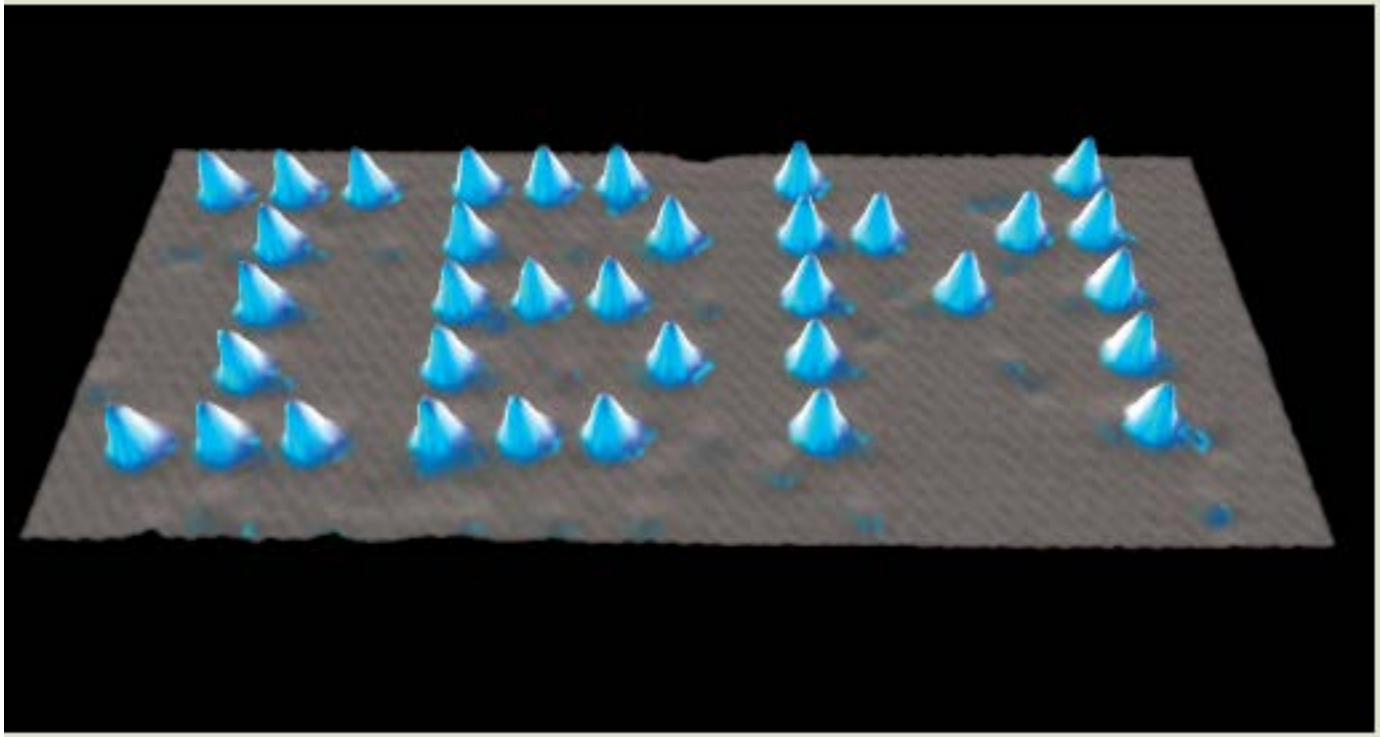
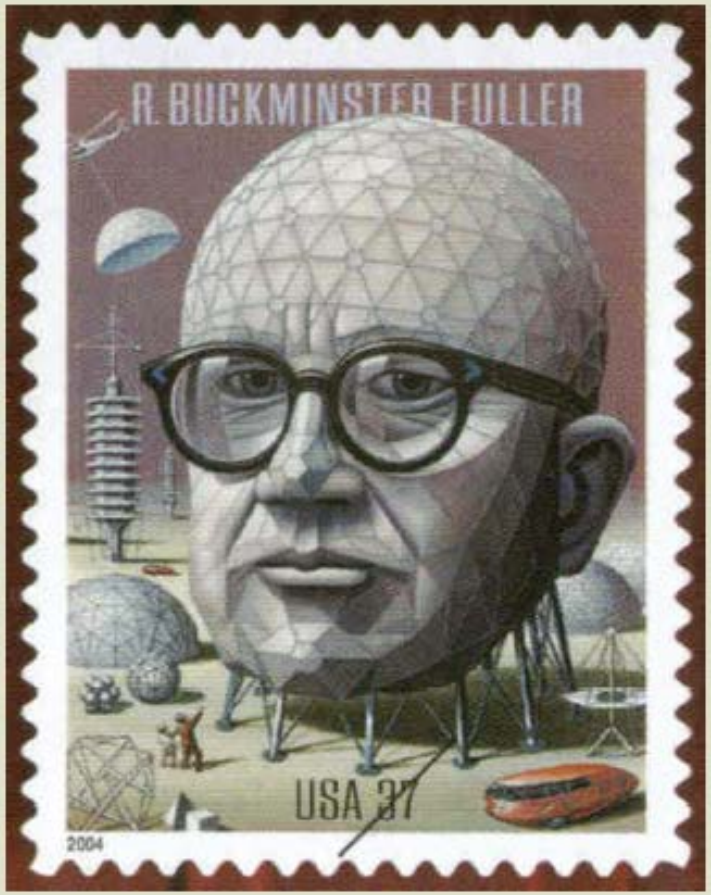


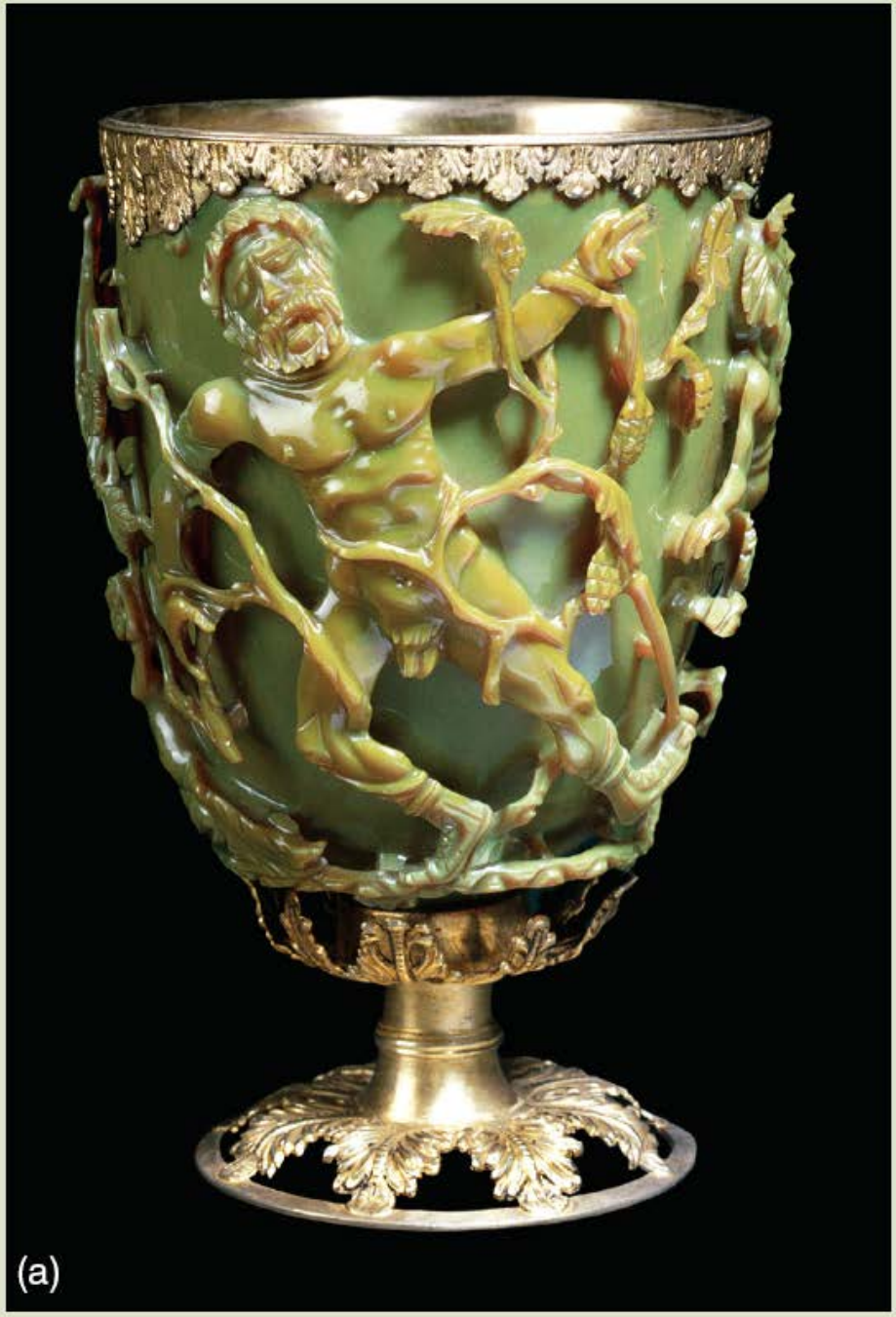
Image reprinted with permission from IBM Research, Almaden Research Center.

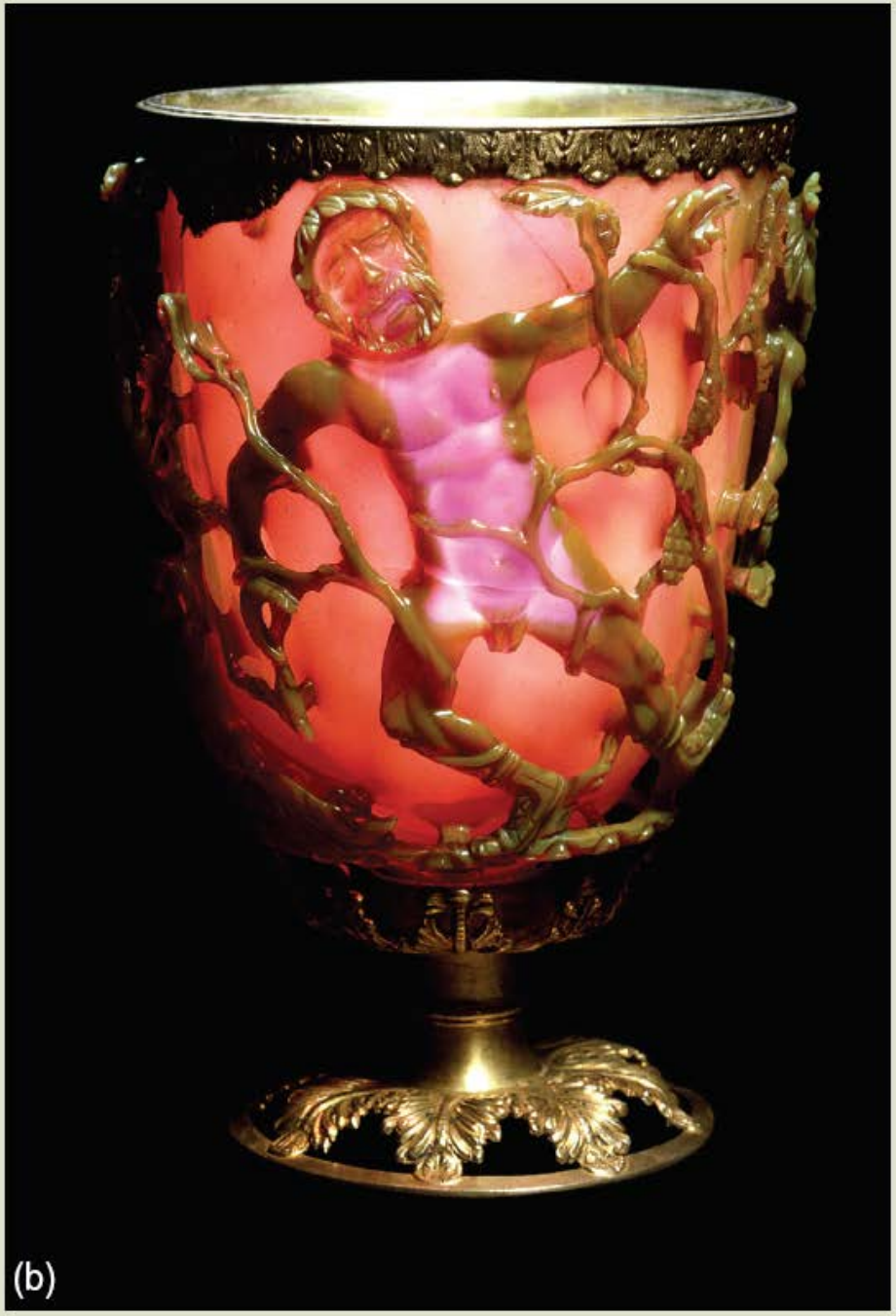
FIG. 1.19

Buckminster Fuller was an architect known for his geodesic dome design. Carbon C_{60} molecules are called buckminster fullerenes in his honor.



Source: Image courtesy of the United States Postal Service. With permission.



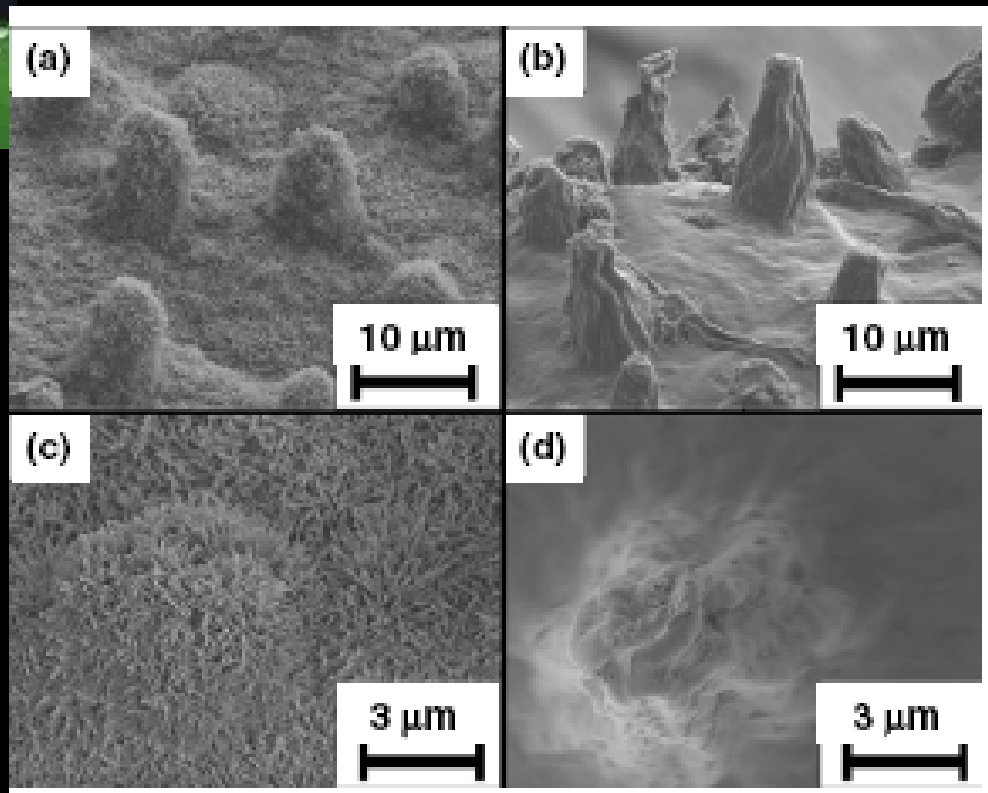


Source: Images reprinted with permission from British Museum Images.

The Lotus Leaf

Multilevel Roughness

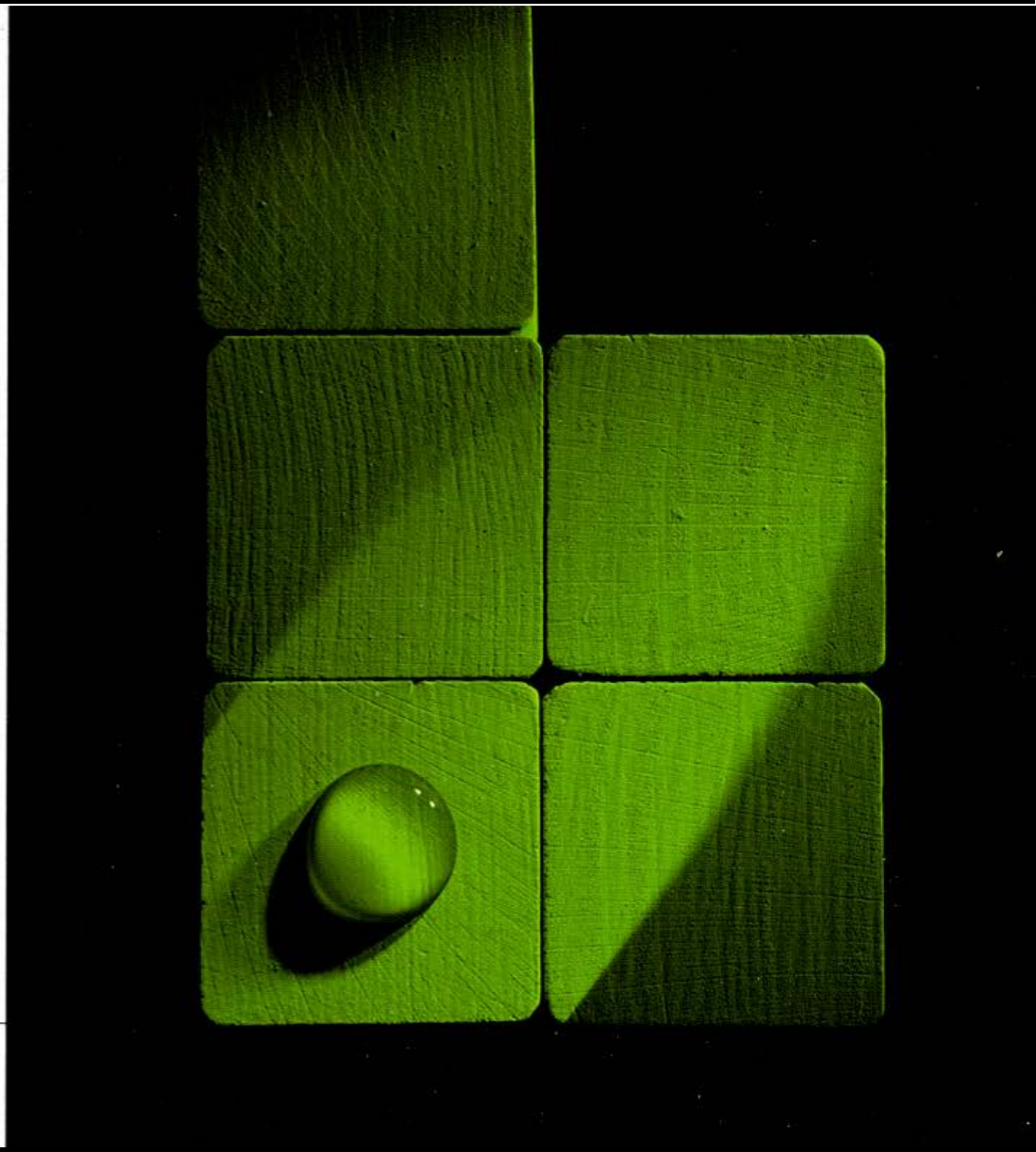
Hydrophobicity



The Lotus Effect

lotus leaf

In 1982 botanist Wilhelm Barthlott of the University of Bonn in Germany discovered in the lotus leaf a naturally self-cleaning, water-repellent surface. The secret lies in waxy microstructures and nanostructures that, by their contact angle with water, cause it to bead and roll away like mercury, gathering dirt as it goes. Barthlott patented his discovery, calling it the Lotus Effect. It has found commercial application in products like the biomimetic paint Lotusan (on blocks at right). Infused with microbumps, the paint is reputed to repel water and resist stains for decades.

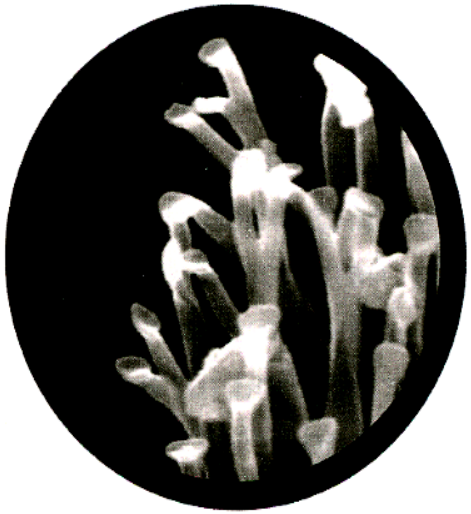


How does the gecko gets its grip?

To see what enables this reptile to cling upside down to a pane of glass, zoom in on its toes (below). Millions of hairs are split into hundreds of tips, each roughly 200 nanometers wide. At this scale a faint intermolecular attraction called the van der Waals force pulls glass and hair tips together. Multiplied millions of times this force creates adhesion that holds the gecko.

GECKO TOES

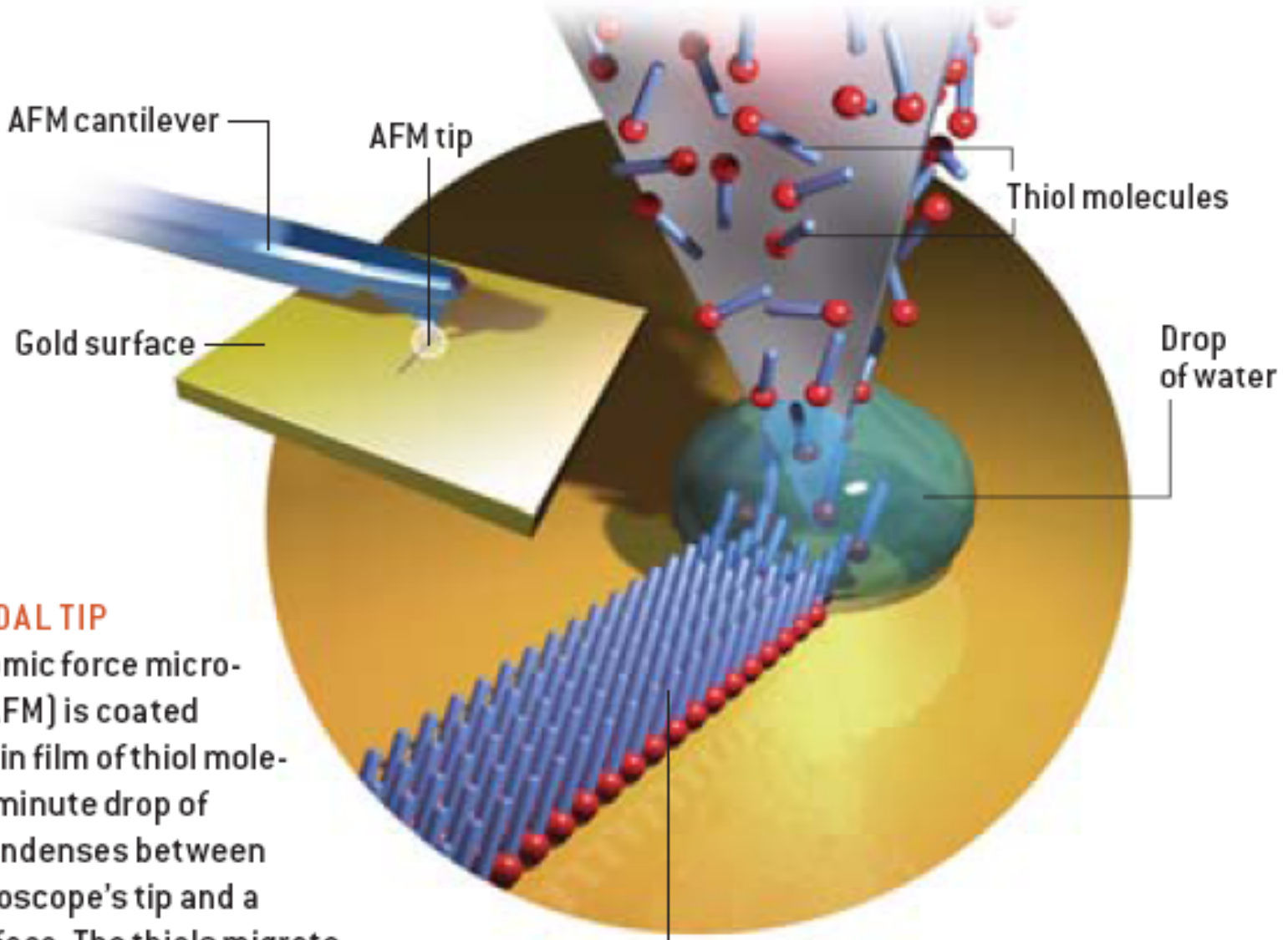
MICROHAIRS (SETAE) ON TOES



NANOHAIRS ON MICROHAIRS

ANDREW SYRED, PHOTO RESEARCHERS, INC. (MIDDLE); KELLAR AUTUMN AND ED FLORANCE, LEWIS & CLARK COLLEGE (RIGHT)

DIP-PEN LITHOGRAPHY



PYRAMIDAL TIP of an atomic force microscope (AFM) is coated with a thin film of thiol molecules. A minute drop of water condenses between the microscope's tip and a gold surface. The thiols migrate from the tip to the surface, where they form a self-assembled monolayer.

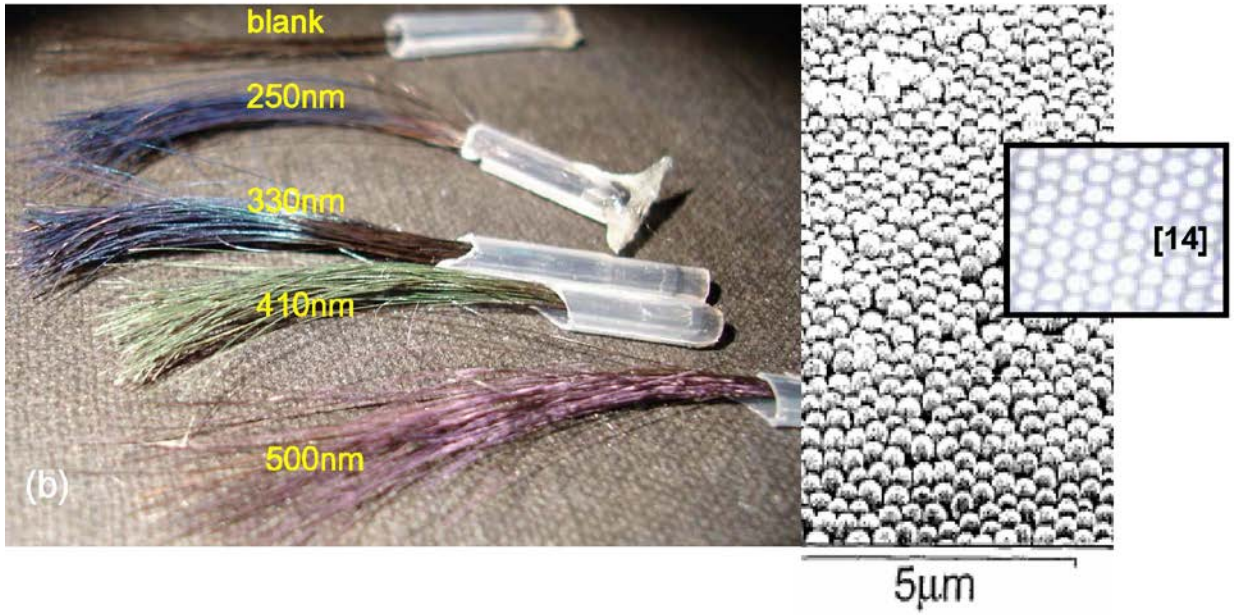
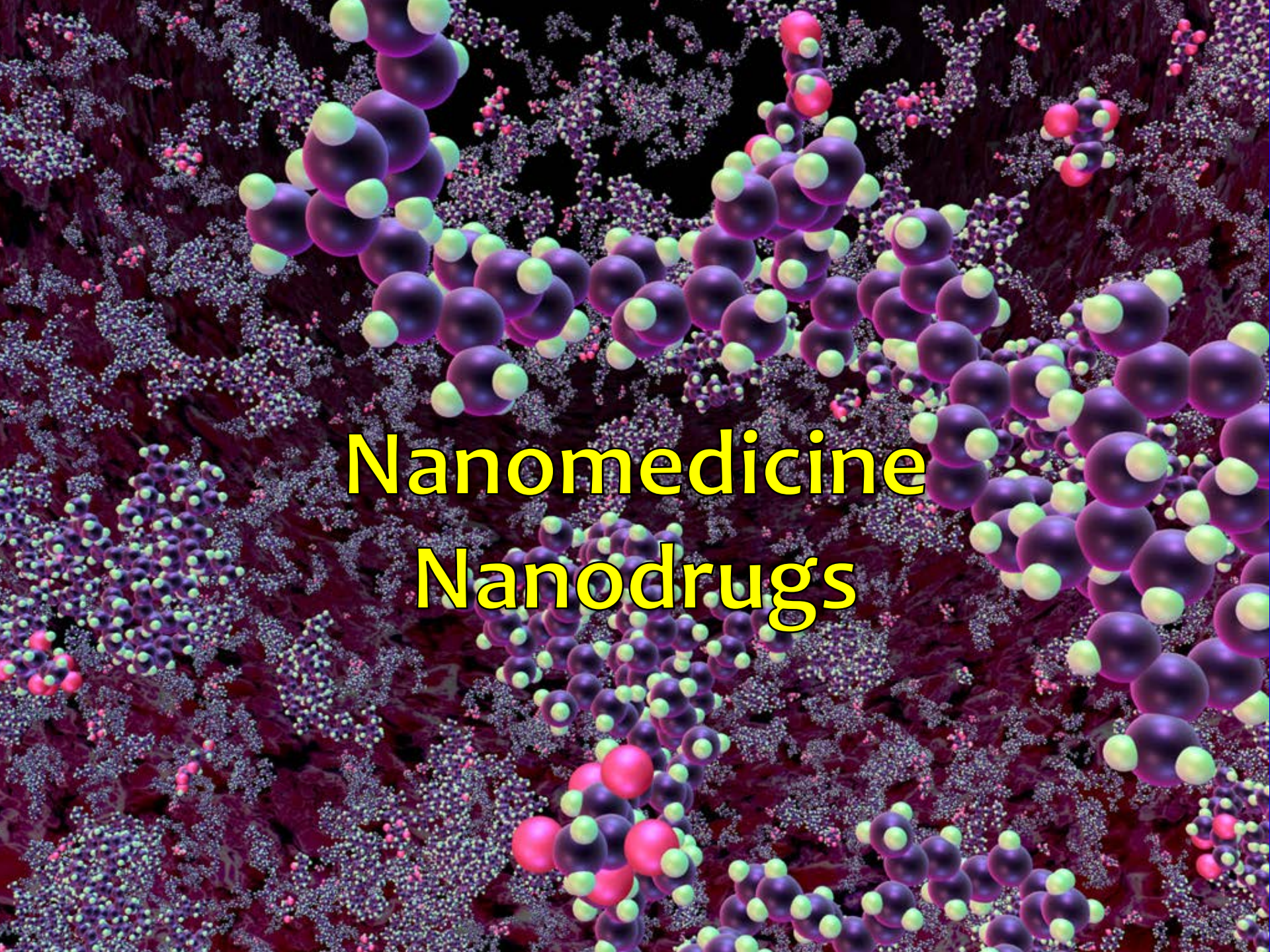


FIGURE XX.6 Photonic cosmetics and "hair jewelry" :

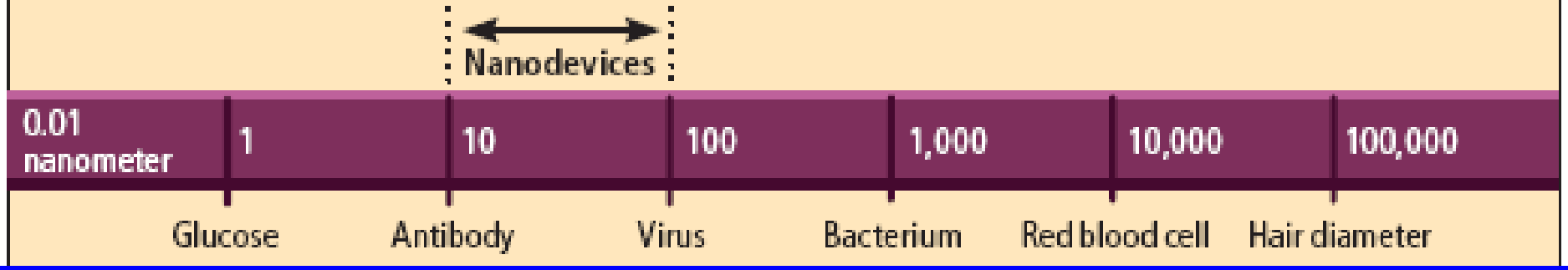
(a) Loreal's announcement of "colourless colour" in cosmetics. The inset shows platelets of nano-scale thickness, producing the colour [10]. (b) Unilever's patented technology for colouring hair by deposition of nano particles as multilayer colloid crystal [17,18]. Inset shows cross section of the iridescent spine of Sea-mouse with similar characteristic lattice dimensions [14]

Superhydrophilic coatings may be used to eliminate fogging from mirrors, lenses, and shower screens. (Courtesy of Tim Kemmitt.)


Nanomedicine
Nanodrugs

NANOTECH IN MEDICINE

At the scale of one nanometer—one billionth of a meter—materials and devices can interact with cells and biological molecules in unique ways. The nanoscale technologies already used in research or therapies are generally between 10 nanometers, the size of an antibody protein, and 100 nanometers, the size of a virus. These devices and particles are being applied as sensors to detect molecules such as proteins or DNA, as imaging enhancers, and as a means to target specific tissues and deliver therapeutic agents.



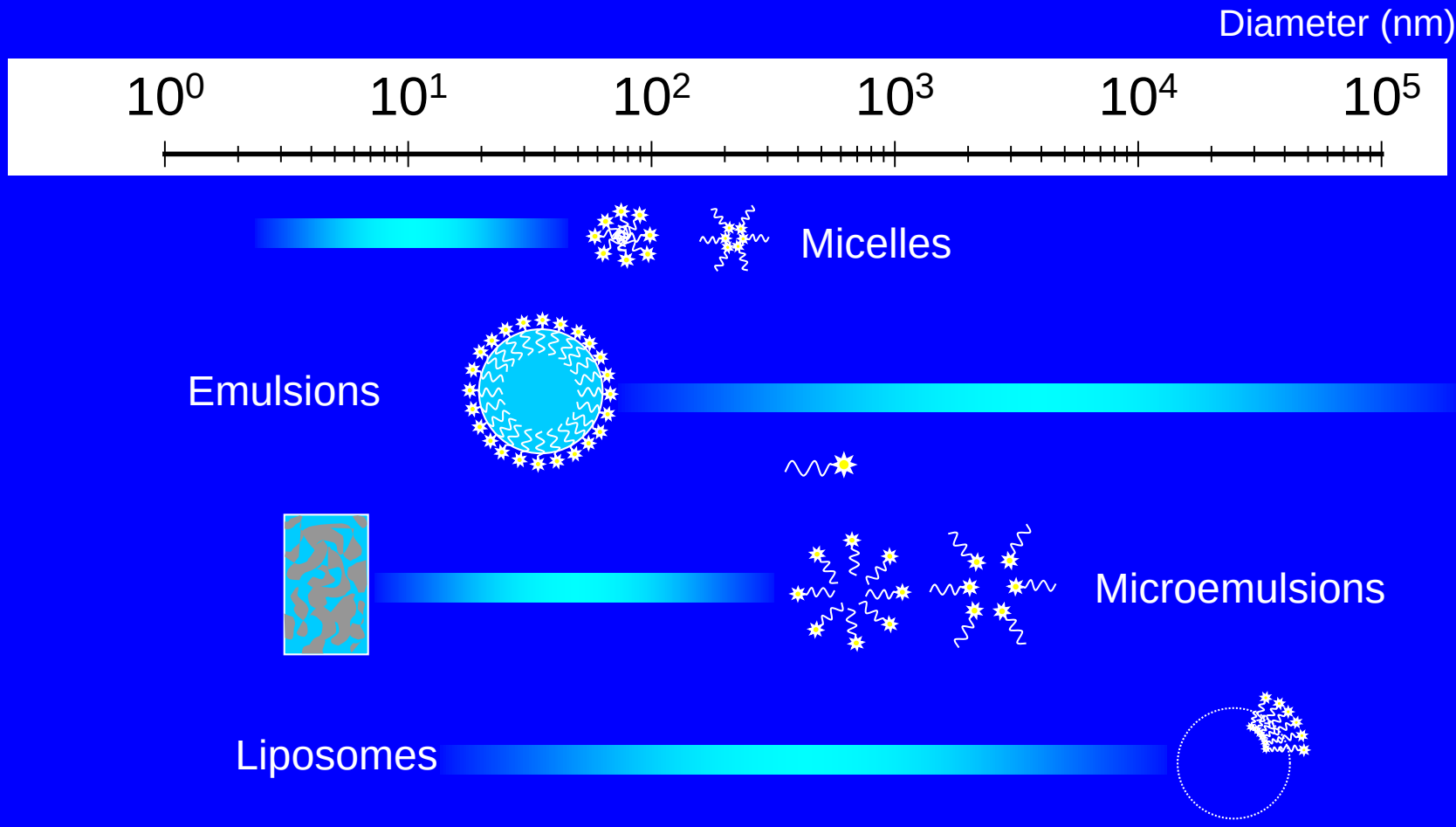
Human health has always been determined on the nanometer scale; this is where the structure and properties of the machines of life work in every one of the cells in every living thing. The practical impact of nanoscience on human health will be huge. - Smalley

Nanomedicine

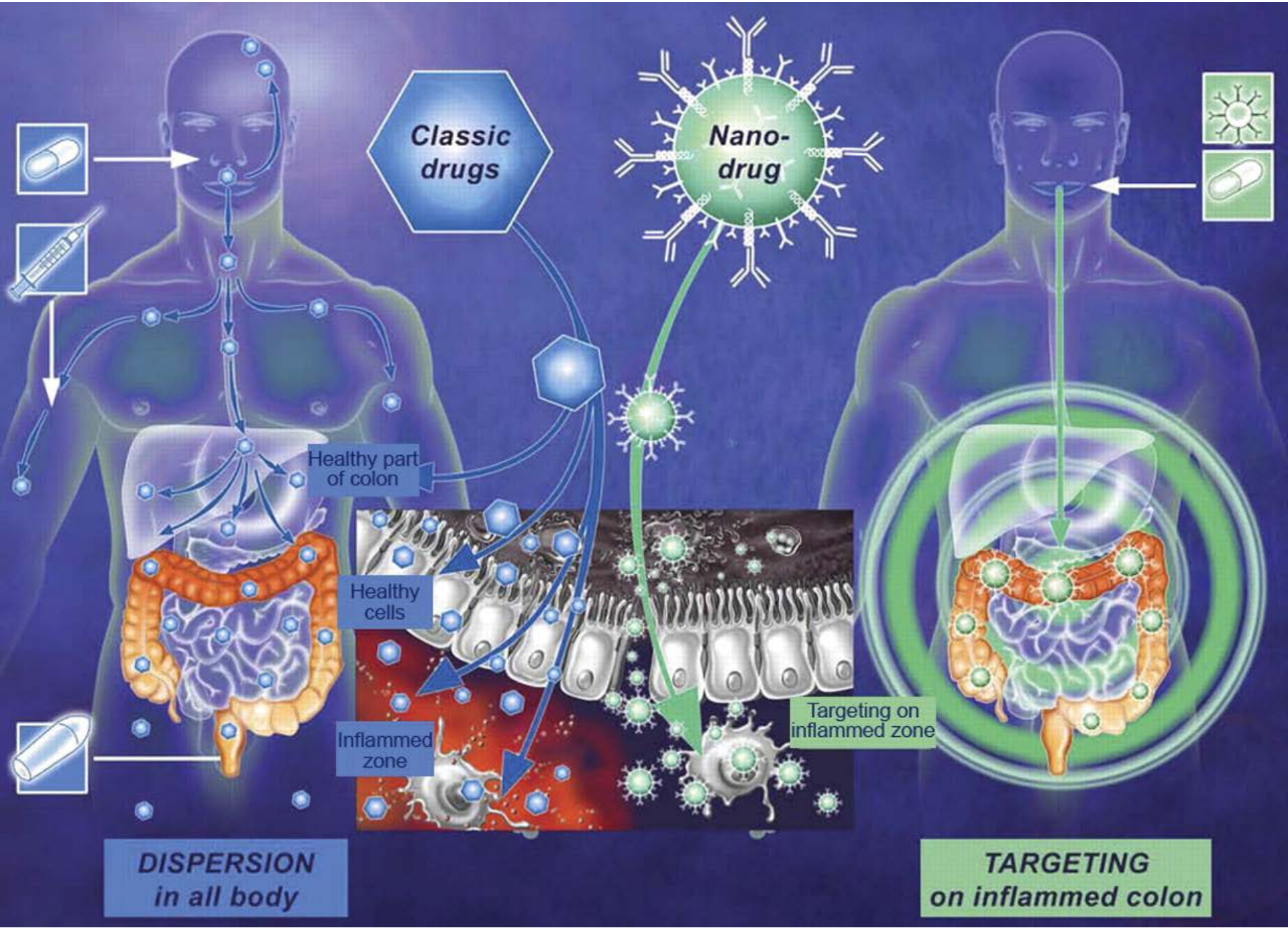
European Science Foundation:

"...the science and technology of diagnosing, treating and preventing disease and traumatic injury, of relieving pain, and of preserving and improving human health, using molecular tools and molecular knowledge of the human body."

Nano: Repackaging of Old Terminology?



Common Theme: "Solubilization"


Classic drugs
Nano-drug
Healthy part of colon
Healthy cells
Inflammed zone
Targeting on inflammed zone
DISPERSION in all body
TARGETING on inflammed colon

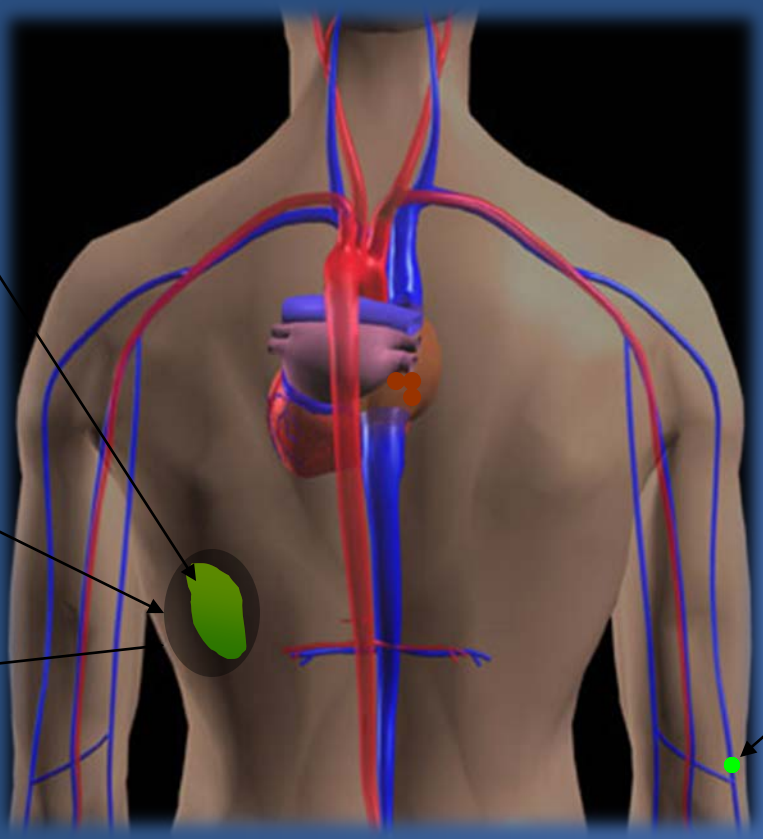
Nano Can Address Lack of Specificity Issues

Precision Medicine: Bench to Bedside

Solid tumor

apply magnetic field to concentrate nanoparticles (NPs)

modulate the magnetic field to release APIs from NPs



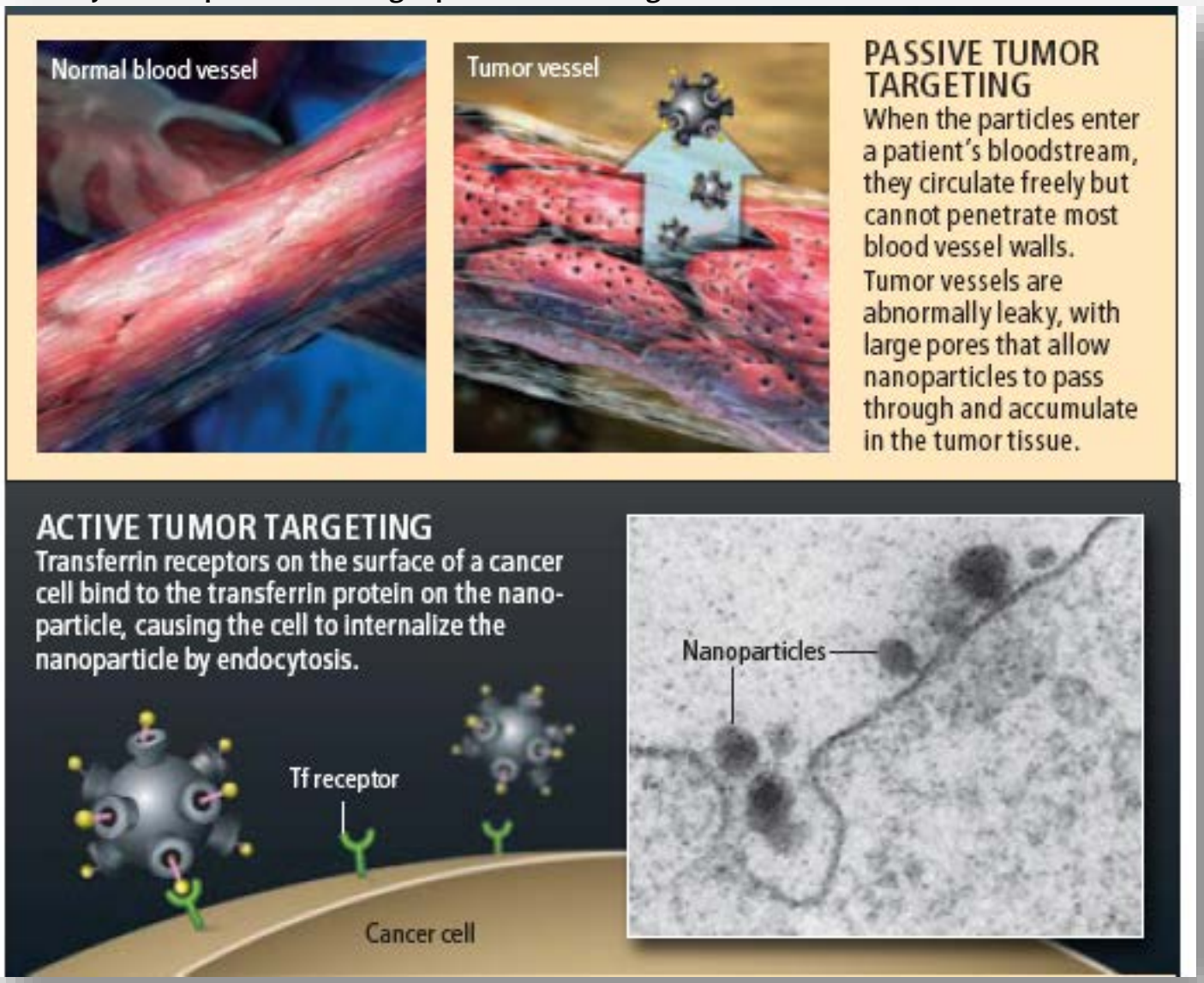
Site-Specific Drug Delivery

<u>Other options for targeting:</u>
-direct injection into tumor site
-coating MNPs with ligands like Abs for site-specific targeting

Inject MNPs intravenously, MNPs will circulate through the blood stream

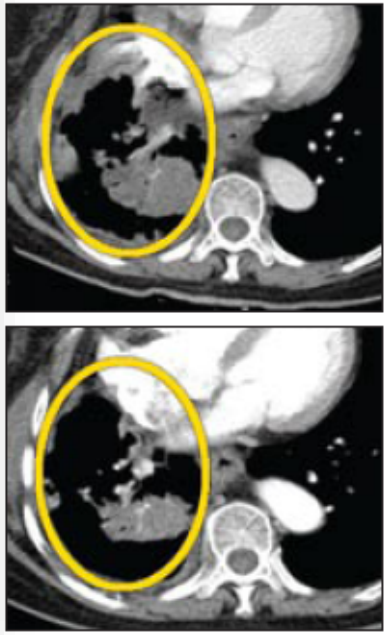
Nano Can Address Lack of Specificity Issues

Enormous R&D is focussed on site-specific delivery of therapeutics -
delivery of therapeutics to the right place and releasing it there in a controlled manner.

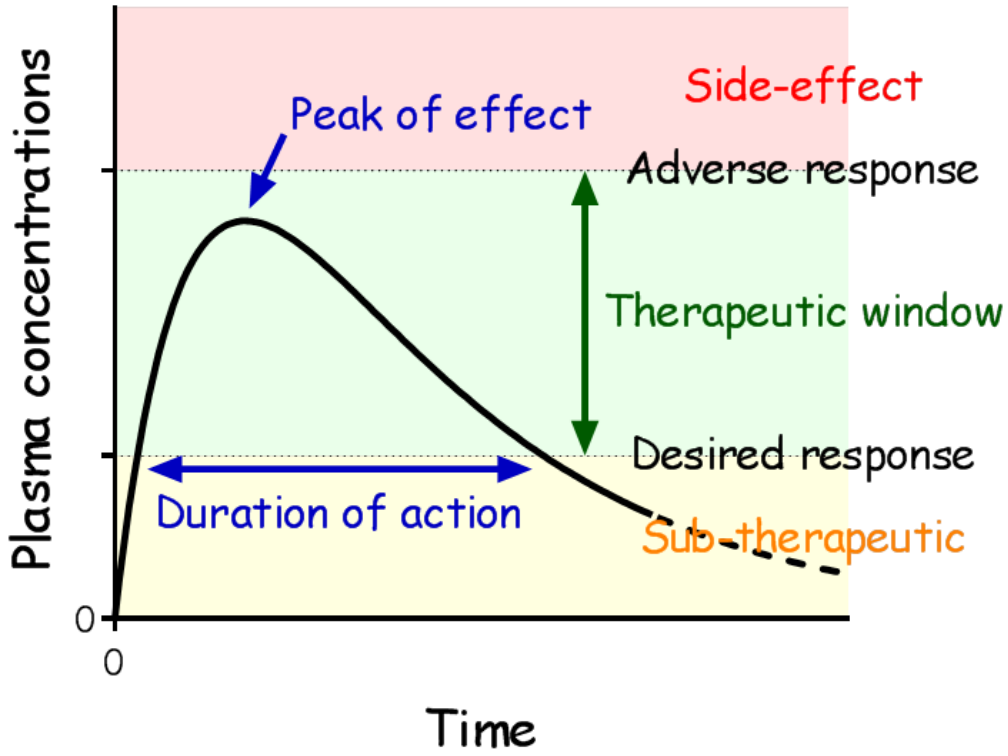


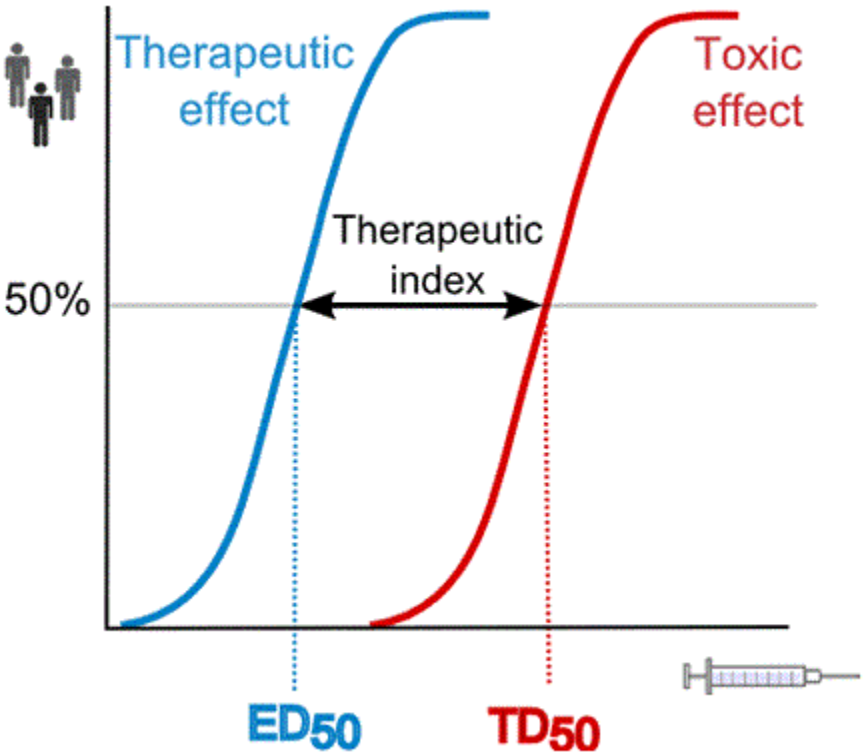
ON TARGET

An experimental nanotherapy, IT-101, encapsulates a chemotherapy drug, camptothecin, inside a nanoparticle designed to circulate for an extended period in the bloodstream and to accumulate in tumors. In a human safety trial, evidence of the treatment's efficacy was seen in some patients with advanced cancers. In the CT scans below, views of a patient's midsection show a large lung tumor (*top, gray circled mass*) before treatment with IT-101 and after six months of treatment (*bottom*), when the tumor had shrunk considerably.



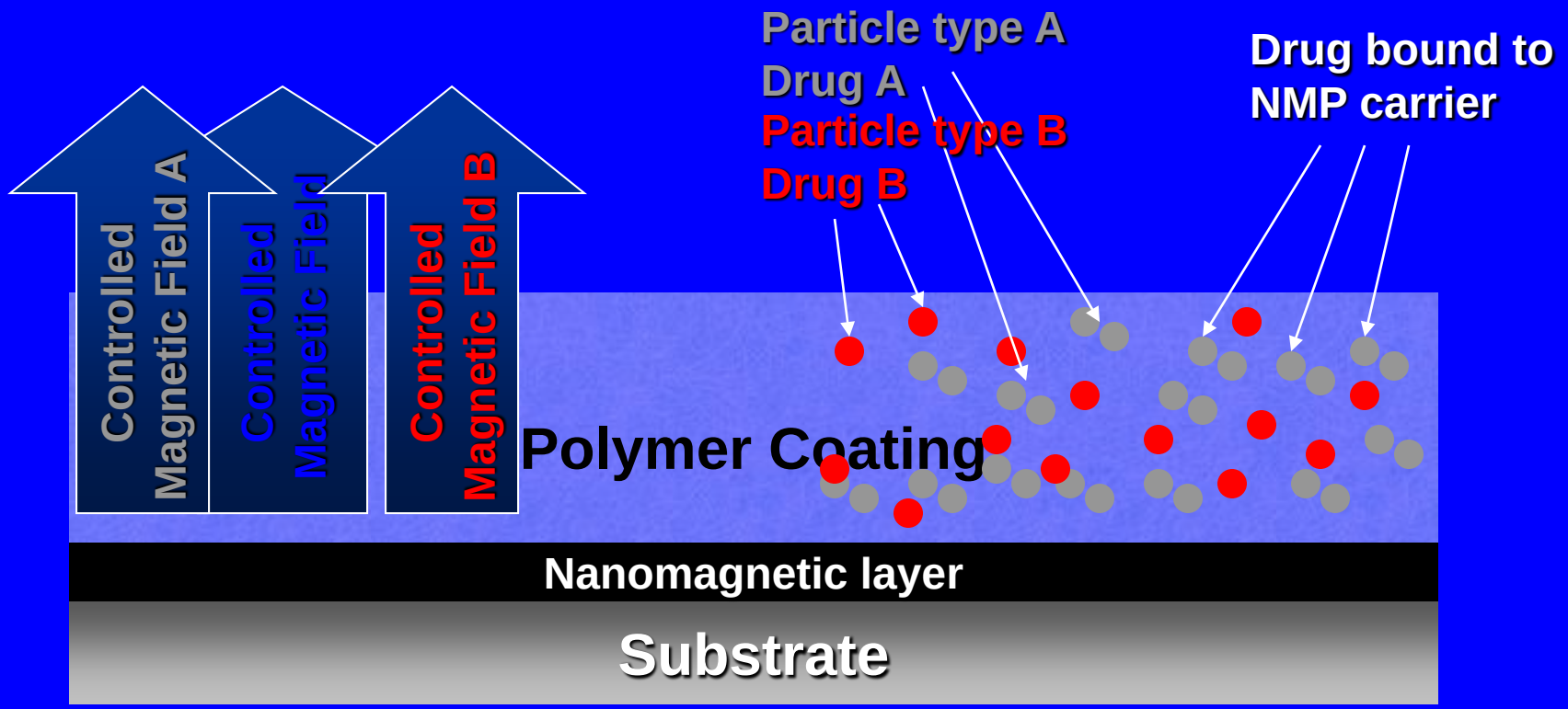
Nano Can Improve the Therapeutic Window





Nano Enables Controlled Manipulation

Surface Elution on Demand - Stents



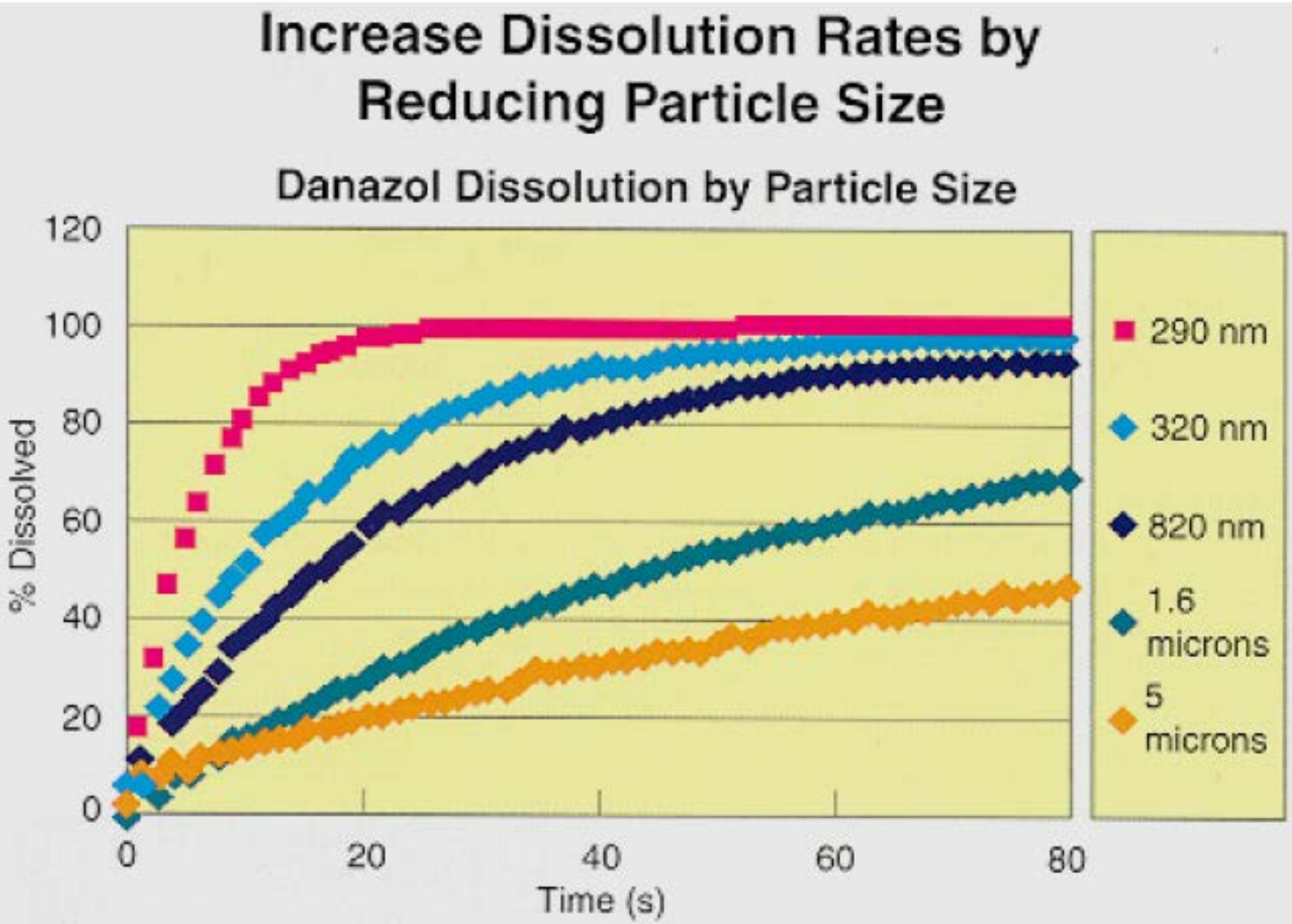
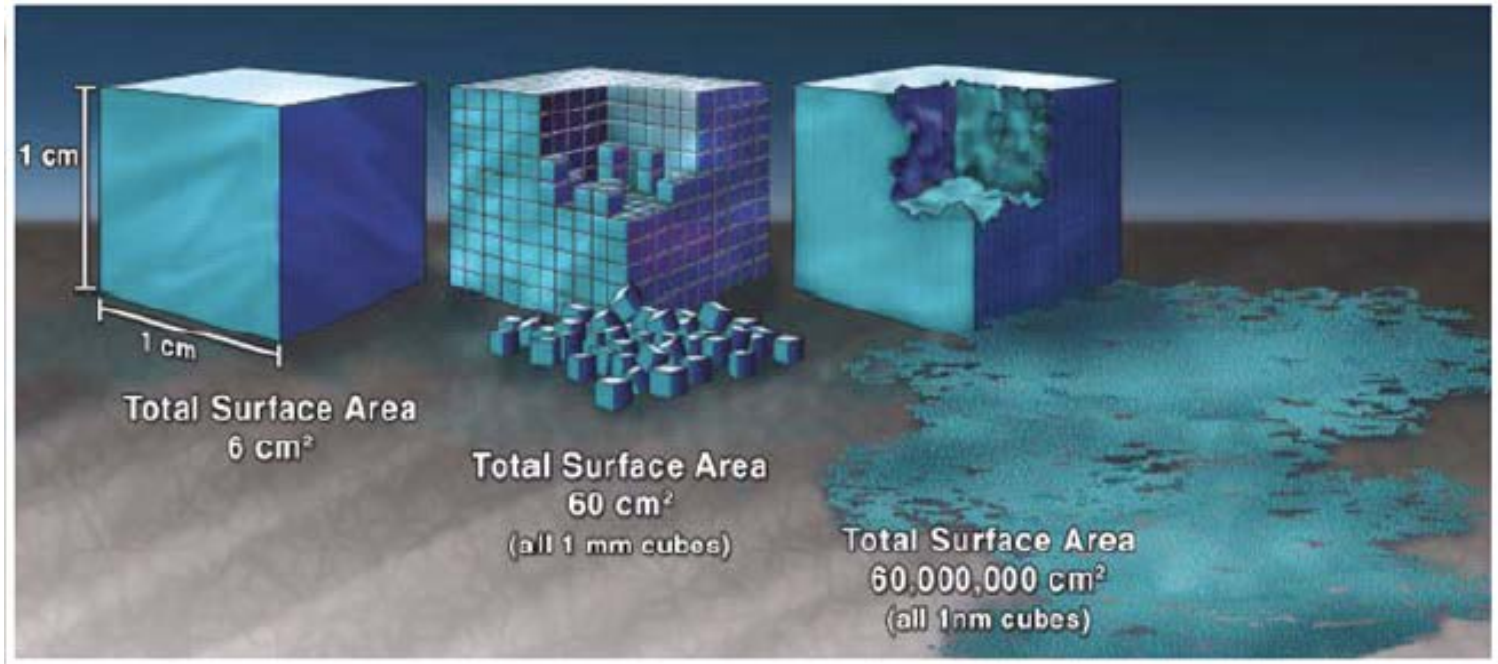
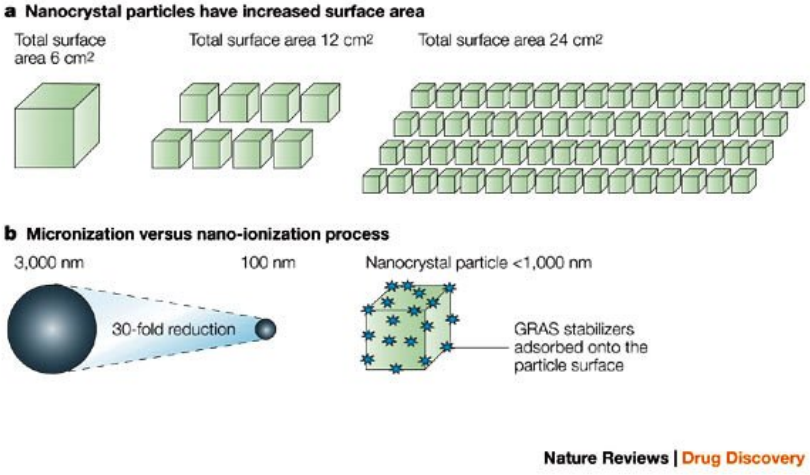


Figure 5.5

Increasing bioavailability (measured by solubility in water) of a medicine upon grinding it to nanoscale size. *Courtesy of Chris Tucker, Dow Chemical Company.*

Nano Can Address Poor Water Solubility Issues



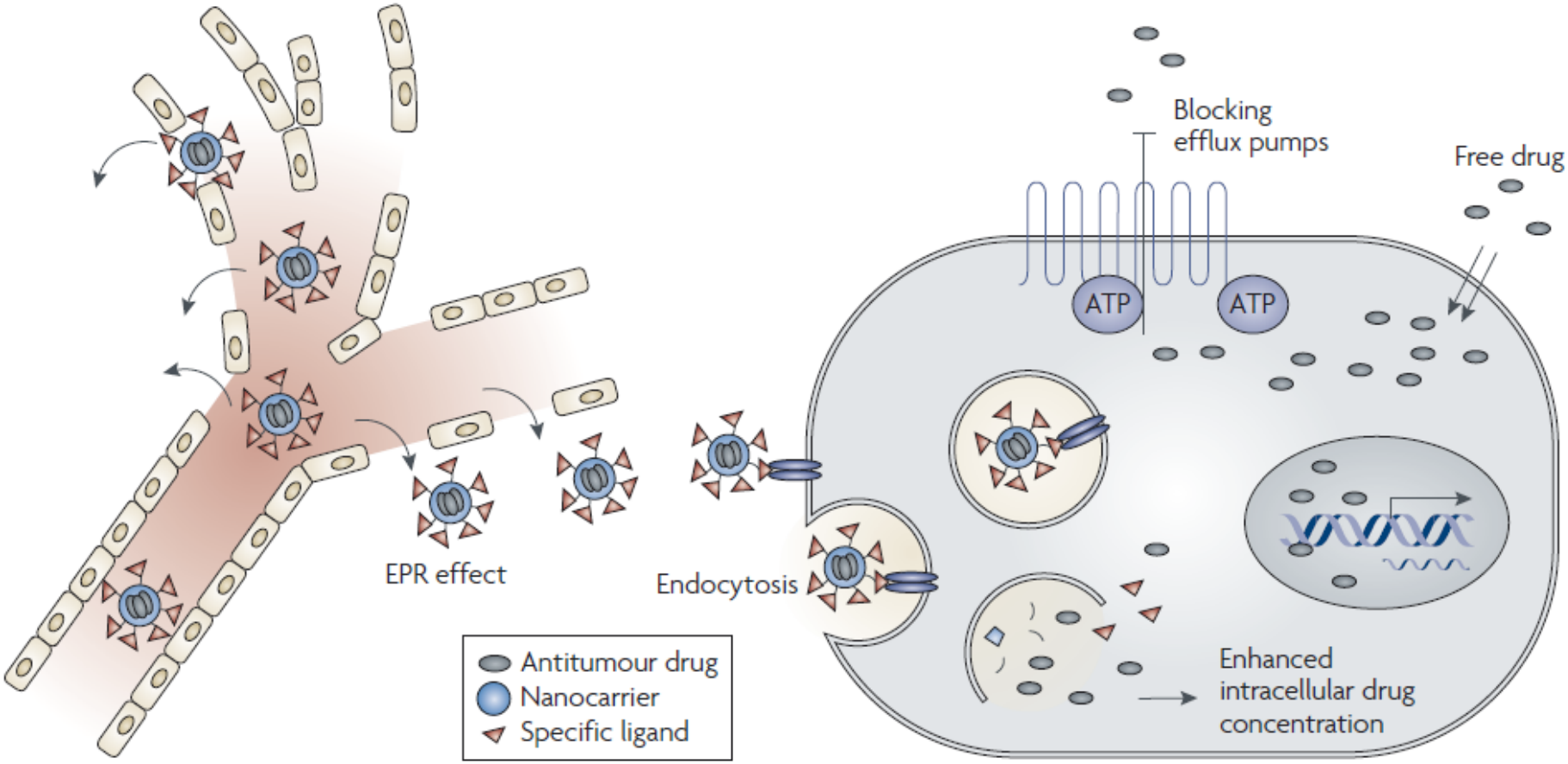


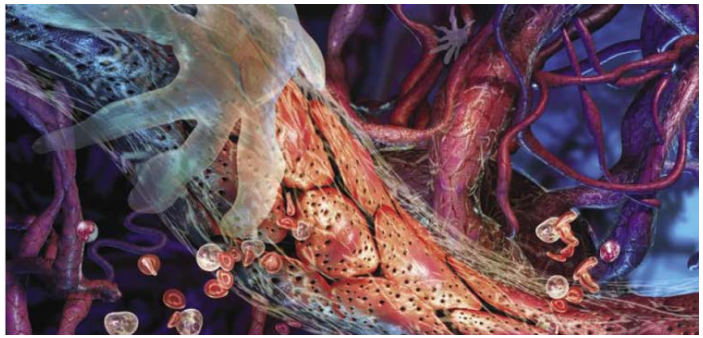
NANOCRYSTAL® TECHNOLOGY

elan

Solubility ↑ Stability ↑ Specificity ↑ Toxicity ↓ Efficacy ↑

Sources: Elan, Nature Group, Bawa Biotech

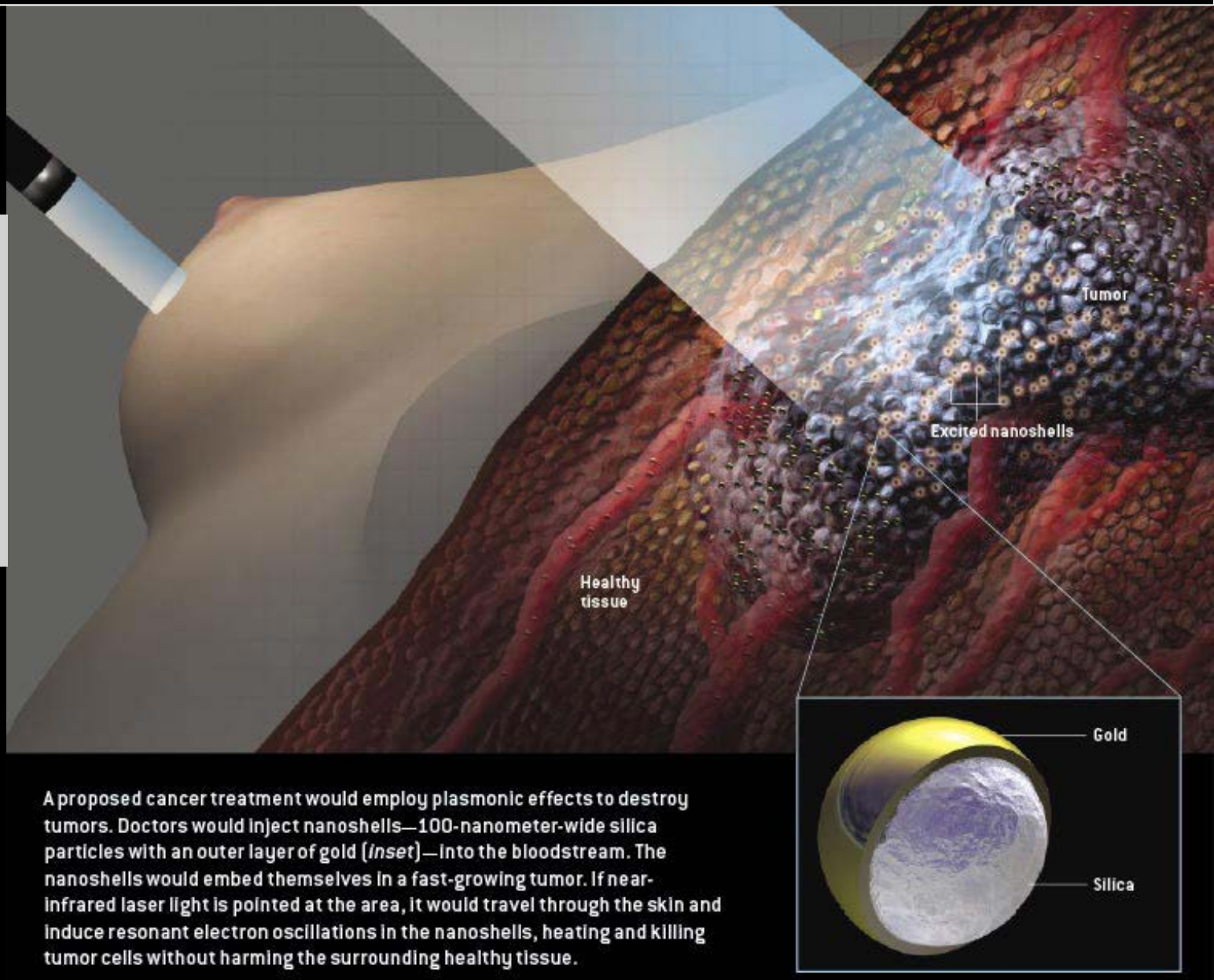




Source: Dr. Mark Davis, CalTech

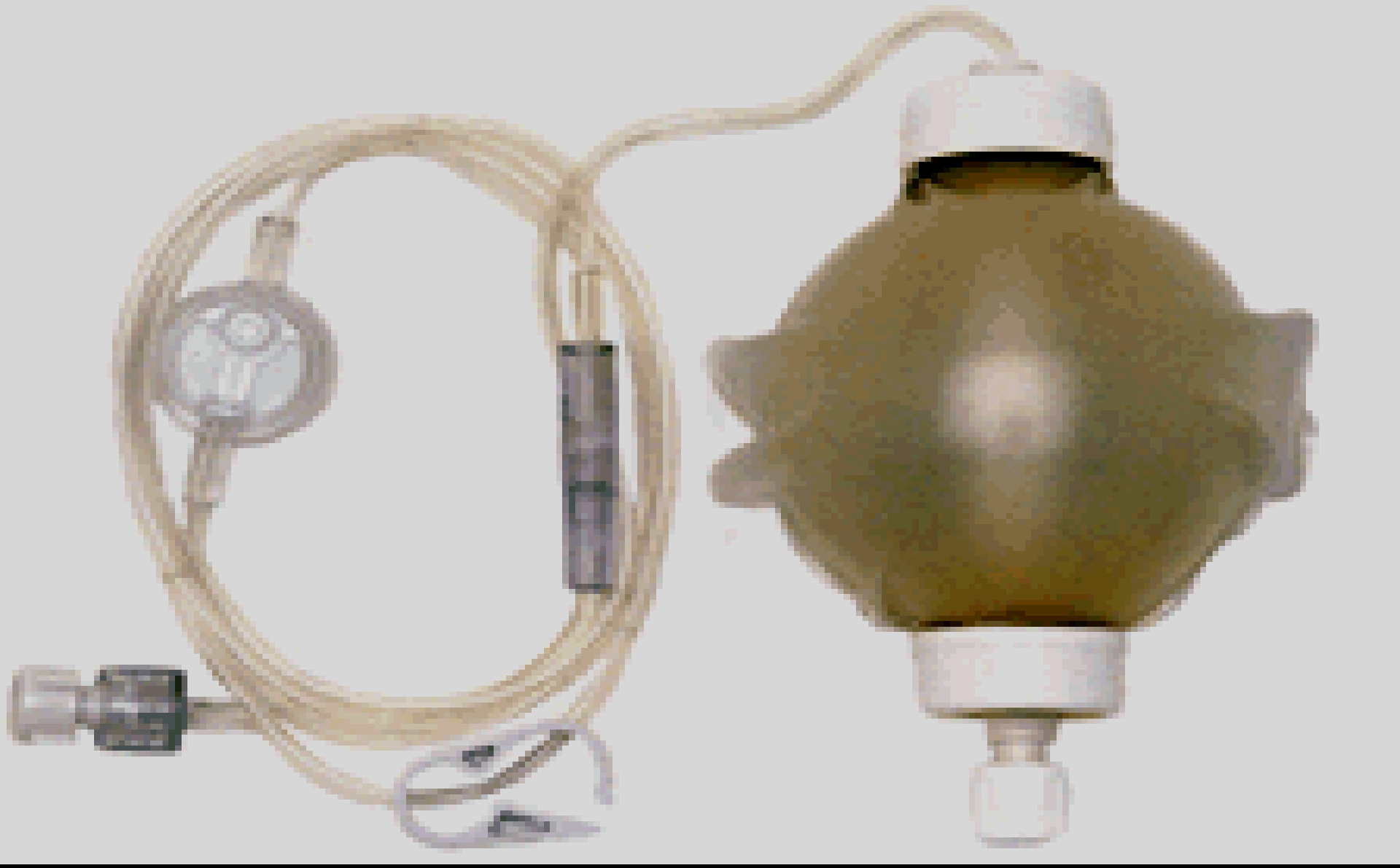
Tumor Busting Capsules

One of the most highly publicized areas of nanomedicine research involves gold nanoshells to detect and treat cancerous tumors.



A proposed cancer treatment would employ plasmonic effects to destroy tumors. Doctors would inject nanoshells—100-nanometer-wide silica particles with an outer layer of gold (*inset*)—into the bloodstream. The nanoshells would embed themselves in a fast-growing tumor. If near-infrared laser light is pointed at the area, it would travel through the skin and induce resonant electron oscillations in the nanoshells, heating and killing tumor cells without harming the surrounding healthy tissue.

Graphic: *Scientific American* PHIL SAUNDERS *Space Channel Ltd.*



Two companies, AcryMed and I-Flow, have collaborated on a surgical catheter for pain relief. What's unique about this device is the silver nanoparticle coating, which was approved by the FDA in Dec 2005 as an inhibitor of infection-causing biofilm.

Nanodrug

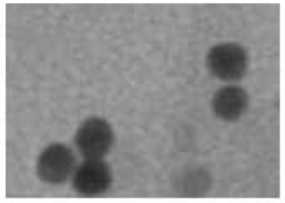
There is no formal definition for a nanotherapeutic (or nanodrug product) formulation. My definition:

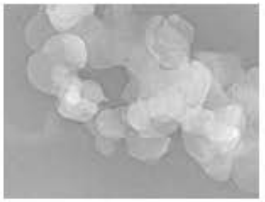
"A nanodrug is: (1) a formulation, often colloidal, containing therapeutic particles (nanoparticles) ranging in size from 1–1,000 nm; and (2) either (a) the carrier(s) is/are the therapeutic (i.e., a conventional therapeutic agent is absent), or (b) the therapeutic is directly coupled (functionalized, solubilized, entrapped, coated, etc.) to a carrier."

Diversity of Nanomaterials

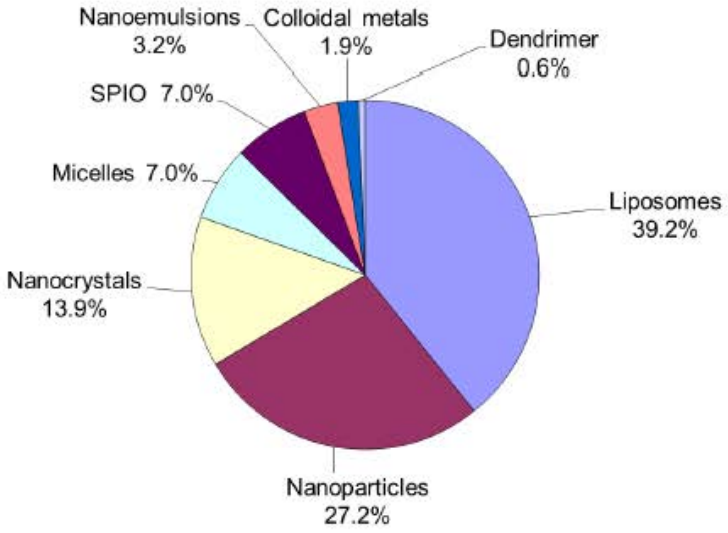
Makes regulatory activities complex

Material

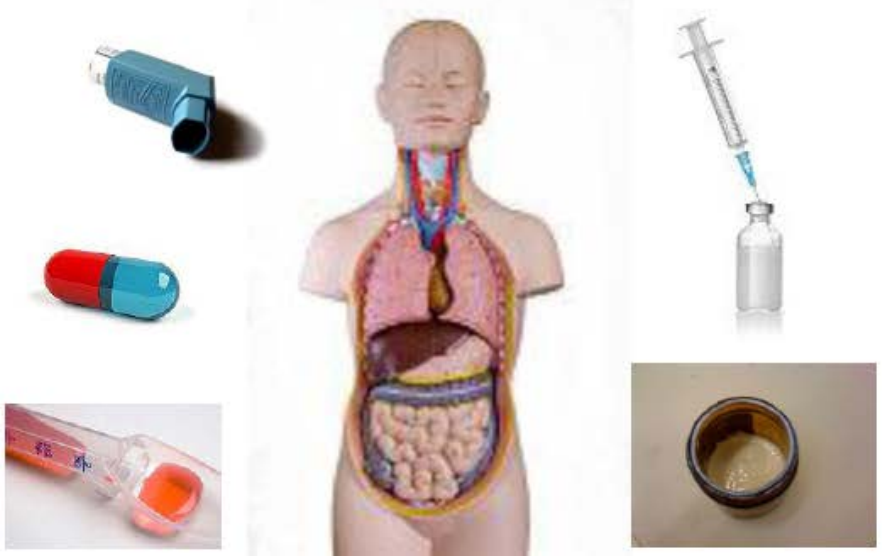




Platform



Route of Administration



Targeting with Magic Bullets

Nanotechnology thinks of molecules as tools = nanomachines, rather than bulk mixtures of randomly interacting entities, as in traditional chemistry.

Paul Ehrlich conceived the idea of drug molecules as "magic bullets" capable of targeting microbes selectively – like the stains used to selectively highlight cells under the 19th century microscopes.

H. Fred Tibbals

Historical Timeline

The prototype of targeted drug delivery can be traced back to the concept of a "magic bullet" that was postulated by Nobel Laureate Paul Ehrlich in 1908 (*magische Kugel*, his term for an ideal therapeutic agent) wherein a pathogenic organism or diseased tissue could be selectively targeted by a drug while leaving healthy cells unharmed. See: Ehrlich, P. (1913). Address in pathology. On chemiotherapy. Delivered before the 17th International Congress of Medicine. *Br. Med. J.*, **16**, 353–359; Witkop, B. (1999).

This concept of a "magic bullet" was realized by the development of antibody-drug conjugates (ADCs) when in 1958 methotrexate was linked to an antibody targeting leukemia cells wherein the antibody component provides specificity for a target antigen and an active agent confers cytotoxicity. It should be noted that, technically, ADCs are NDDS. The first FDA-approved nanotherapeutic was Doxil while AmBisome was the first one approved EMA.

It should be noted, however, that a nanoparticulate iron oxide intravenous solution in the market since the 1960s and certain nanoliposomal products approved in the 1950s and later should, in fact, be considered true first nanomedicines.

In October 2011, One of the major drugs whose supply was deficient in the US was Doxil, and to curb this shortage, the FDA authorized the temporary importation of Lipodox in February 2012. In 2013, Lipodox became the first generic nanodrug approved in the US.

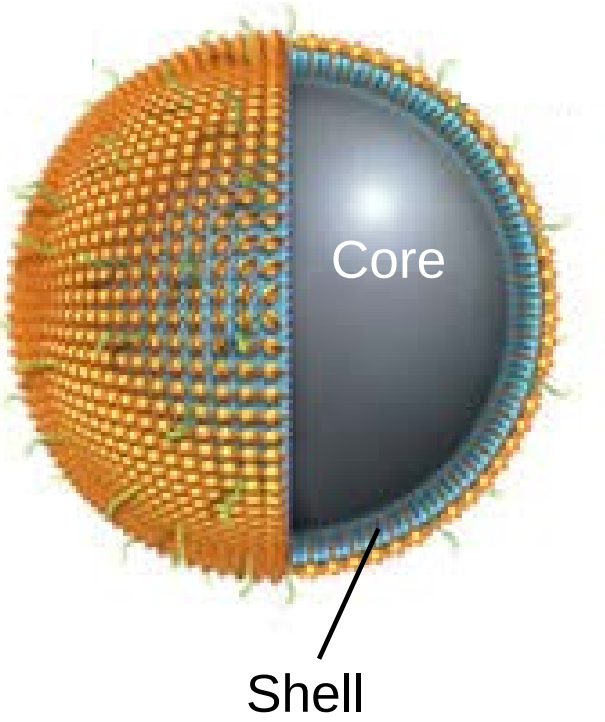
Nanoparticles

Components

Core	Shell
Lipid	Lipid
Drug	Nonionic Surf.
Polymer	Ionic Surf.
Protein	Nothing
Combination	Drug
Nothing	Polymer
Drug	Protein
	Combination

Structure

Core	Shell
Homogeneous	Crystalline
Heterogeneous	Amorphous
Layered	Monolayer
Crystalline	Bilayer
Amorphous	Higher Order
Dense	Mobile
Solid	Immobile
Liquid	



Drug

Core	Shell
Drug *is* Core	Drug *is* Shell
Embedded	Adsorbed
Layered	Intercalated
Covalent	(depth)
Dissolved	Covalent
	Electrostatic
	Hydrophobic

Role

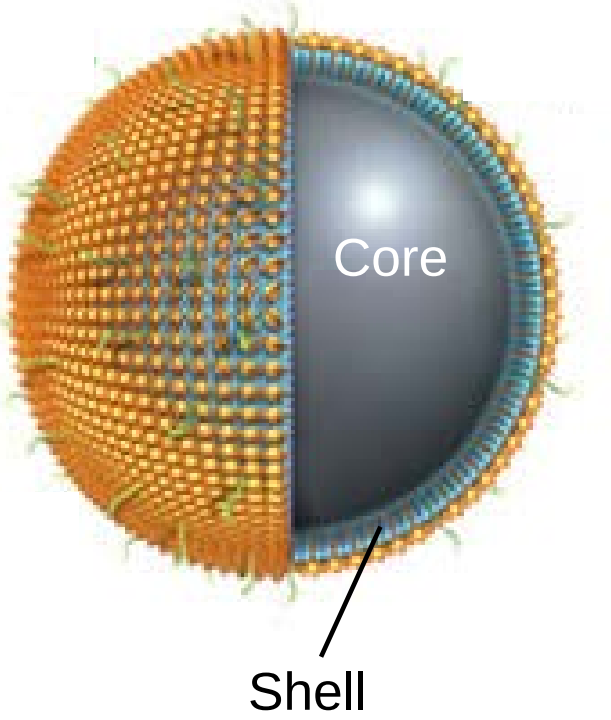
Core	Shell
Repository	Repository
Release	Targeting
Activity (ΔG↑)	PK
	Release
	Bioadesion
	Encapsulate

Nanoparticles

Components

Core	Shell
Lipid	Lipid
Drug	**Nonionic Surf.**
Polymer	Ionic Surf.
Protein	Nothing
Combination	Drug
Nothing	**Polymer**
Drug	Protein
	Combination

Nanocrystal (Emend)



Structure

Core	Shell
Homogeneous	Crystalline
Heterogeneous	Amorphous
Layered	**Monolayer**
Crystalline	Bilayer
Amorphous	Higher Order
Dense	Mobile
Solid	**Immobile**
Liquid	

Drug

Core	Shell
Drug *is* Core	Drug *is* Shell
Embedded	Adsorbed
Layered	Intercalated
Covalent	(depth)
Dissolved	Covalent
	Electrostatic
	Hydrophobic

Role

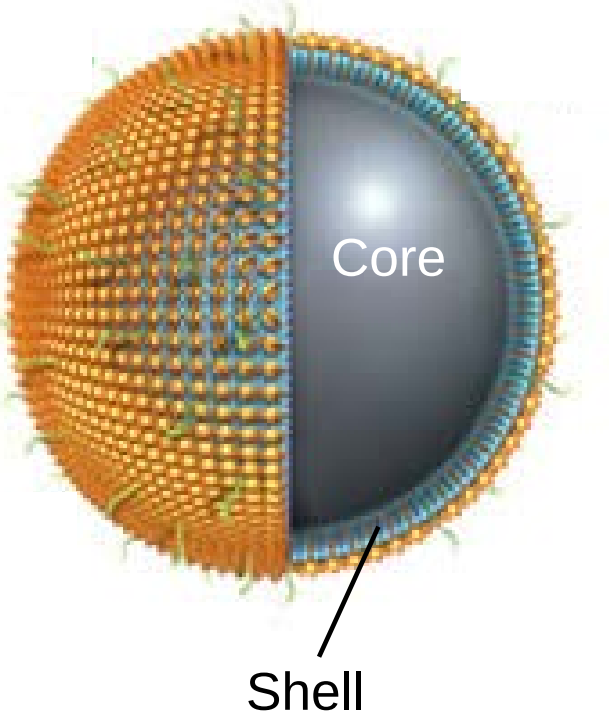
Core	Shell
Repository	Repository
Release	Targeting
Activity (ΔG↑)	**PK**
	Release
	Bioadesion
	Encapsulate

Nanoparticles: Structure

Components

Core	Shell
Lipid	**Lipid**
Drug	Nonionic Surf.
Polymer	Ionic Surf.
Protein	Nothing
Combination	Drug
Nothing	Polymer
Drug	Protein
	Combination

Liposome (AmBisome)



Structure

Core	Shell
Homogeneous	**Crystalline(/)**
Heterogeneous	Amorphous
Layered	Monolayer
Crystalline	Bilayer
Amorphous	Higher Order
Dense	Mobile
Solid	Immobile
Liquid	

Drug

Core	Shell
Drug *is* Core	Drug *is* Shell
Embedded	Adsorbed
Layered	**Intercalated**
Covalent	(depth)
Dissolved	Covalent
	Electrostatic
	Hydrophobic

Role

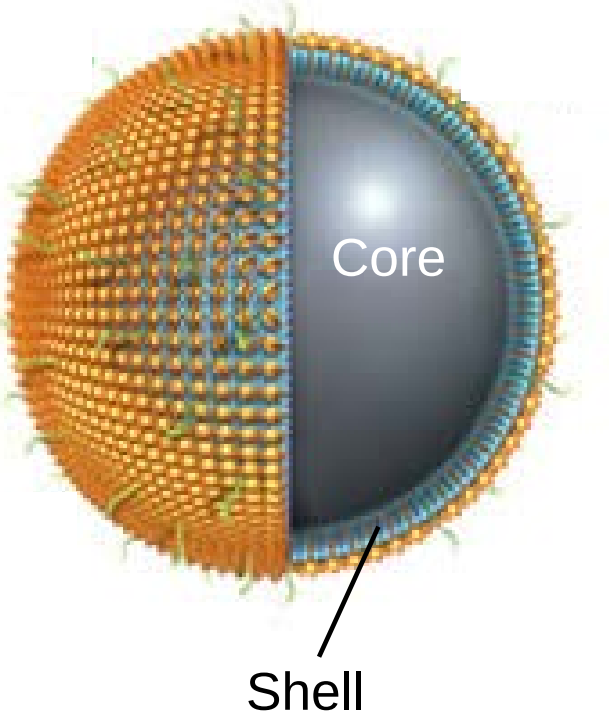
Core	Shell
Repository	Repository
Release	Targeting
Activity (ΔG↑)	**PK**
	Release
	Bioadesion
	Encapsulate

Nanoparticles

Components

Core	Shell
Lipid	Lipid
Drug	Nonionic Surf.
Polymer	Ionic Surf.
Protein	Nothing
Combination	Drug
Nothing	Polymer
Drug	**Protein**
	Combination

Nanoparticle (Abraxane)



Structure

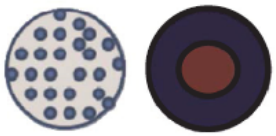
Core	Shell
Homogeneous	Crystalline
Heterogeneous	Amorphous
Layered	Monolayer
Crystalline	Bilayer
Amorphous	Higher Order
Dense	**Mobile**
Solid	Immobile
Liquid	

Drug

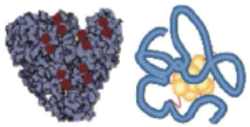
Core	Shell
Drug *is* Core	Drug *is* Shell
Embedded	Adsorbed
Layered	Intercalated
Covalent	(depth)
Dissolved	Covalent
	Electrostatic
	Hydrophobic

Role

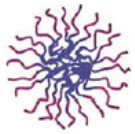
Core	Shell
Repository	Repository
Release	**Targeting**
Activity (ΔG↑)	PK
	Release
	Bioadesion
	Encapsulate



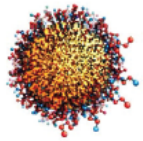
Solid Nanoparticles



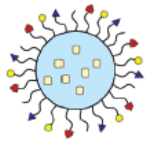
Drug-Polymer Conjugate



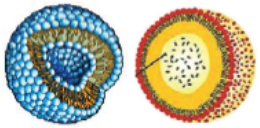
Polymeric Micelle



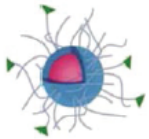
Functionalized Gold NP



Biomimetic NP

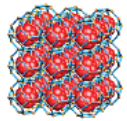


Ligand-Functionalized Nanoliposomes



Ultrasmall Silica Nanoparticle (C Dot)

Drug-Encapsulated Dendrimer

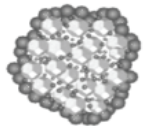


Drug-Loaded NMOFs

Polymer-Polypeptide Conjugate

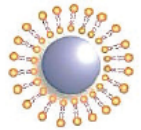
GRAS-Stabilized Nanocrystal

Silica Gold Nanoshell

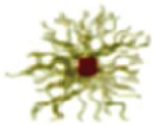


Functionalized Nanodiamonds

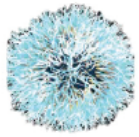
Polymeric Nanoparticle



Phospholipid-Coated Magnetic NP

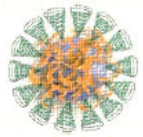


Dextran-Coated USPION

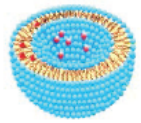


Self-Assembling Peptides

Drug-Loaded Bioinspired Bile Micelle

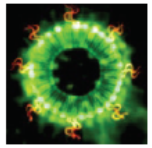


Drug-Loaded Chitosan-PEG Coated Nanogel



Drug-Loaded Nanoliposome

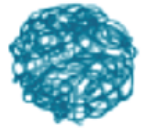
Nanonized API



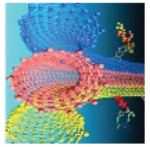
Peptide-siRNA Liposome

Stealth Pegylated Nanoliposome

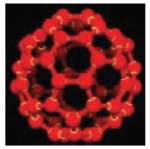
Functionalized Drug Magnetic NP



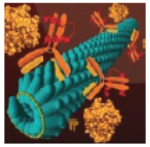
Nanogel



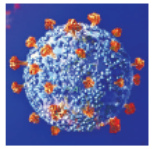
Peptide f-CNTs



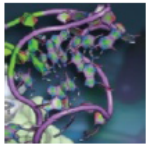
C_{60} Buckminsterfullerene



Enzyme Nanocarrier



Functionalized Solid NP



Aptamers

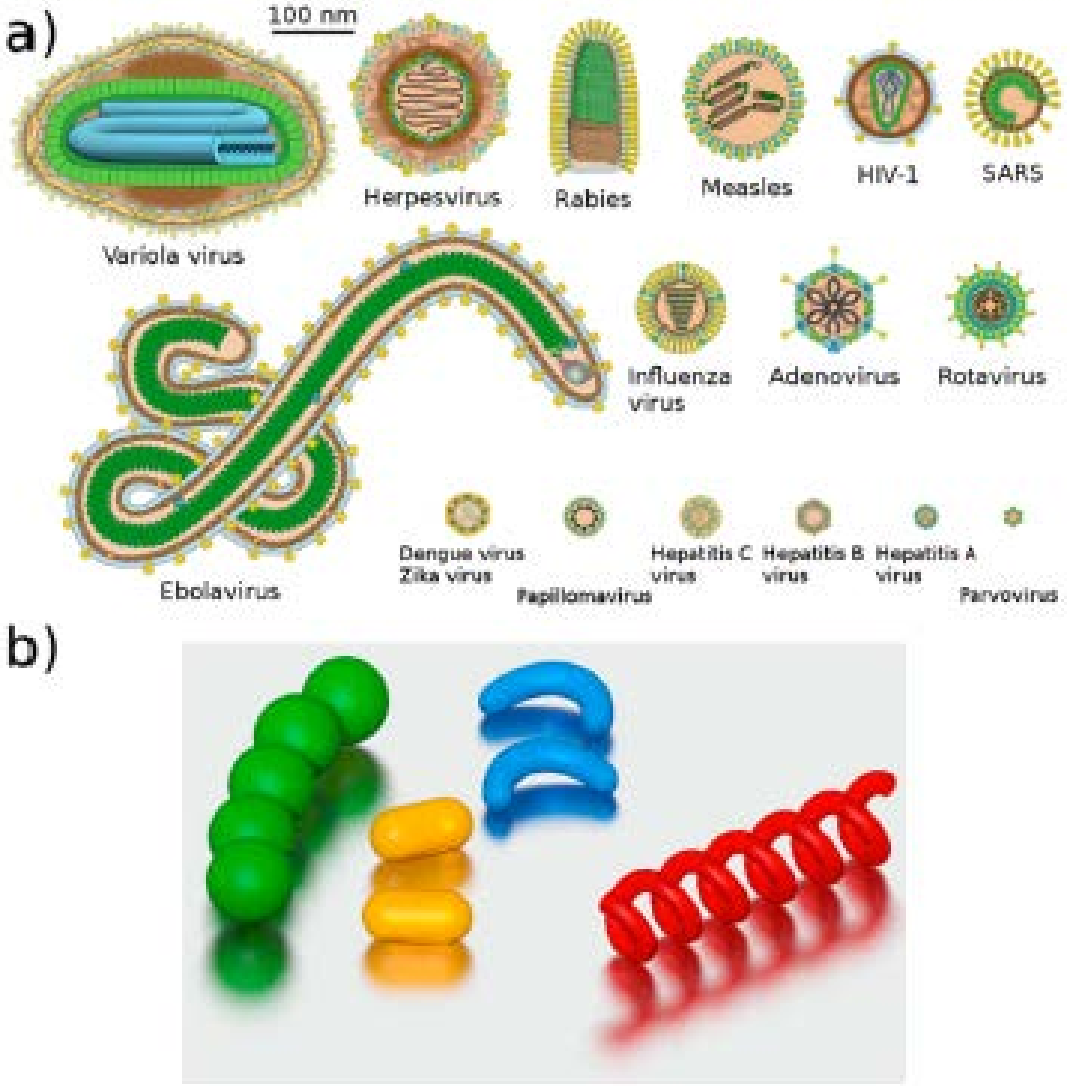


Figure 2. Various morphologies of viruses and bacteria in nature. (a) Schematic of viruses to scale, including brick-shaped or pleomorphic, spherical, bullet-shaped, icosahedral, and filamentous forms. Reprinted with permission from ViralZone, SIB Swiss Institute of Bioinformatics. (b) Common bacterial forms such as spherical (coccus), rod like (bacillus), crescent (vibrio), and twisted (spirillum).

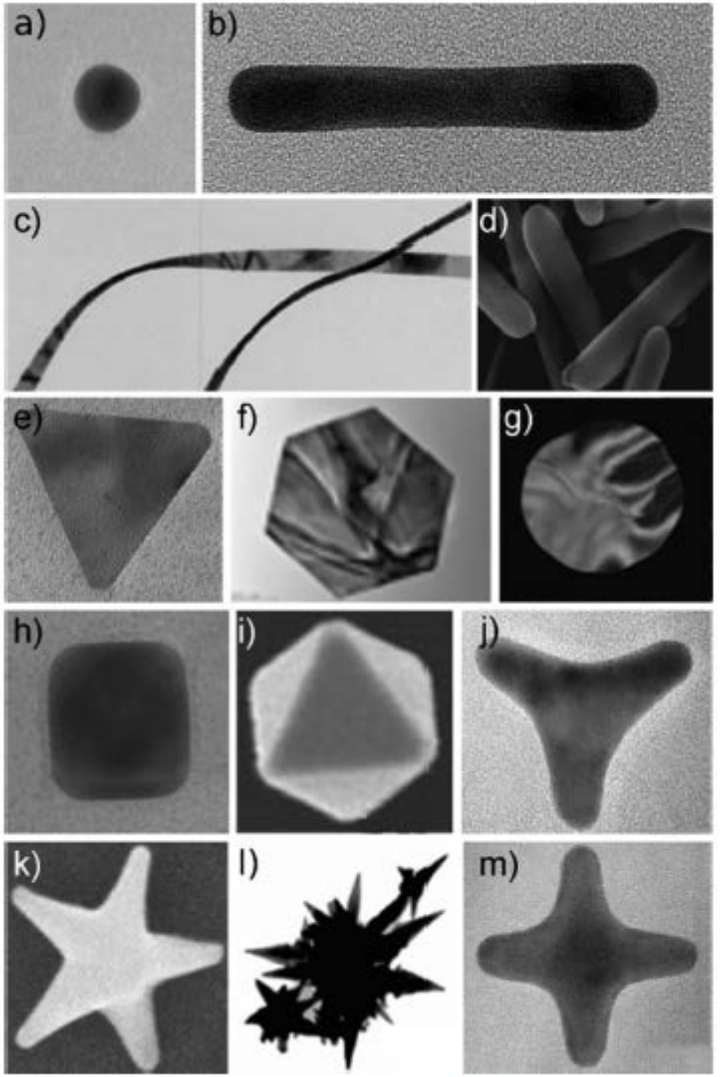


Figure 1. Metallic NPs with various morphologies: (a) nanosphere, (b) nanorod, (c) nanobelt, (d) nanowires, (e) 2D triangle, (f) 2D hexagon, (g) disc, (h) nanocube, (i) octahedron, (j) tripod, (k) nanostar, (l) nanothron, (m) tetrapod. (c, d, e, f, g, j, and m) Adapted with permission from refs 9, 10, 11, 1213, and 14, respectively. Copyright 2008, 2003, 2007, 2005, 2005, and 2003 American Chemical Society, respectively. (k, l) Adapted with permission from ref 15. Copyright 2008 John Wiley and Sons. (i) Reprinted by permission from Macmillan Publishers Ltd.: ref 16, copyright 2007. Some figures have had the background removed for clarity; for original figures and scale bars, see the relevant references.

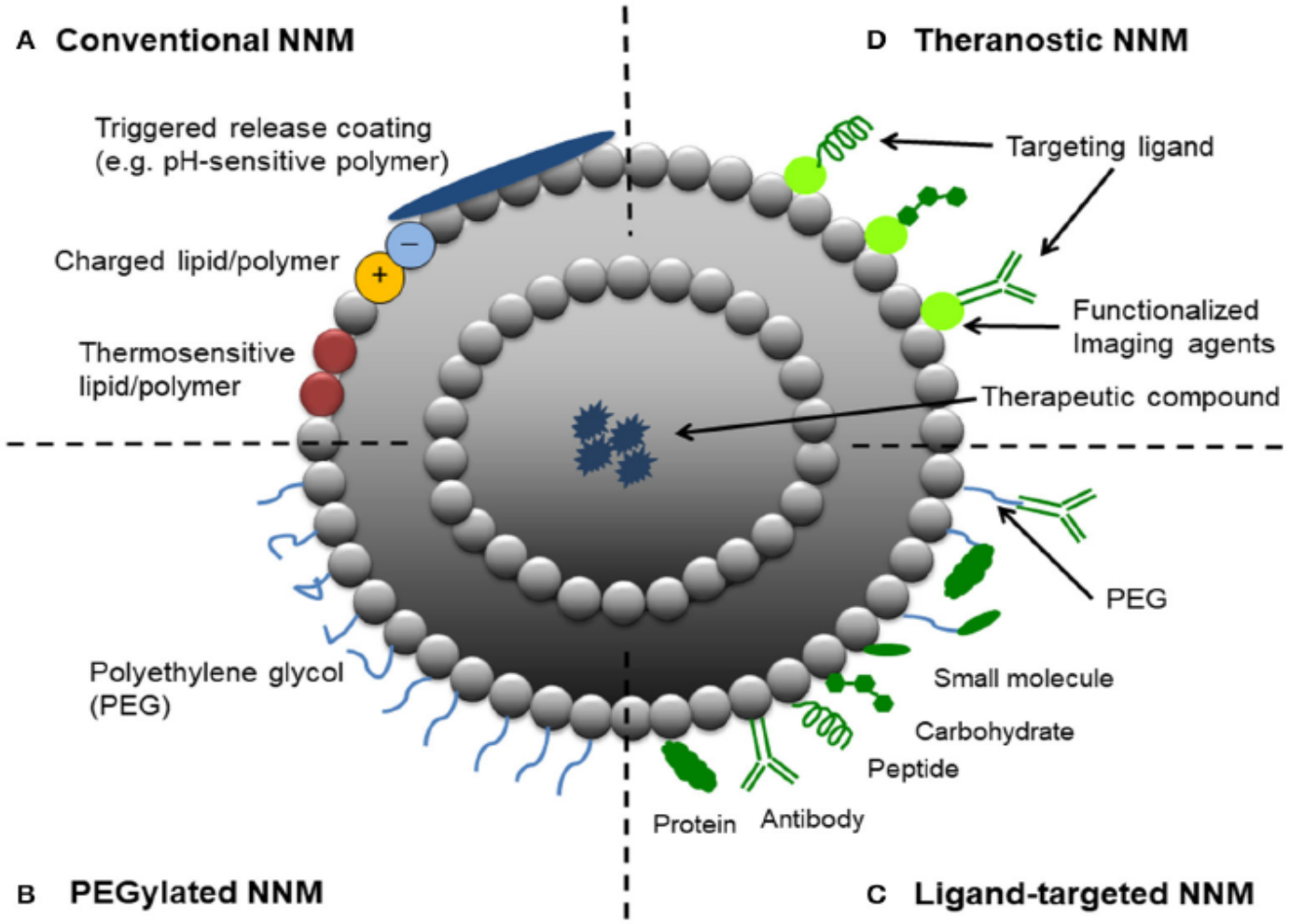
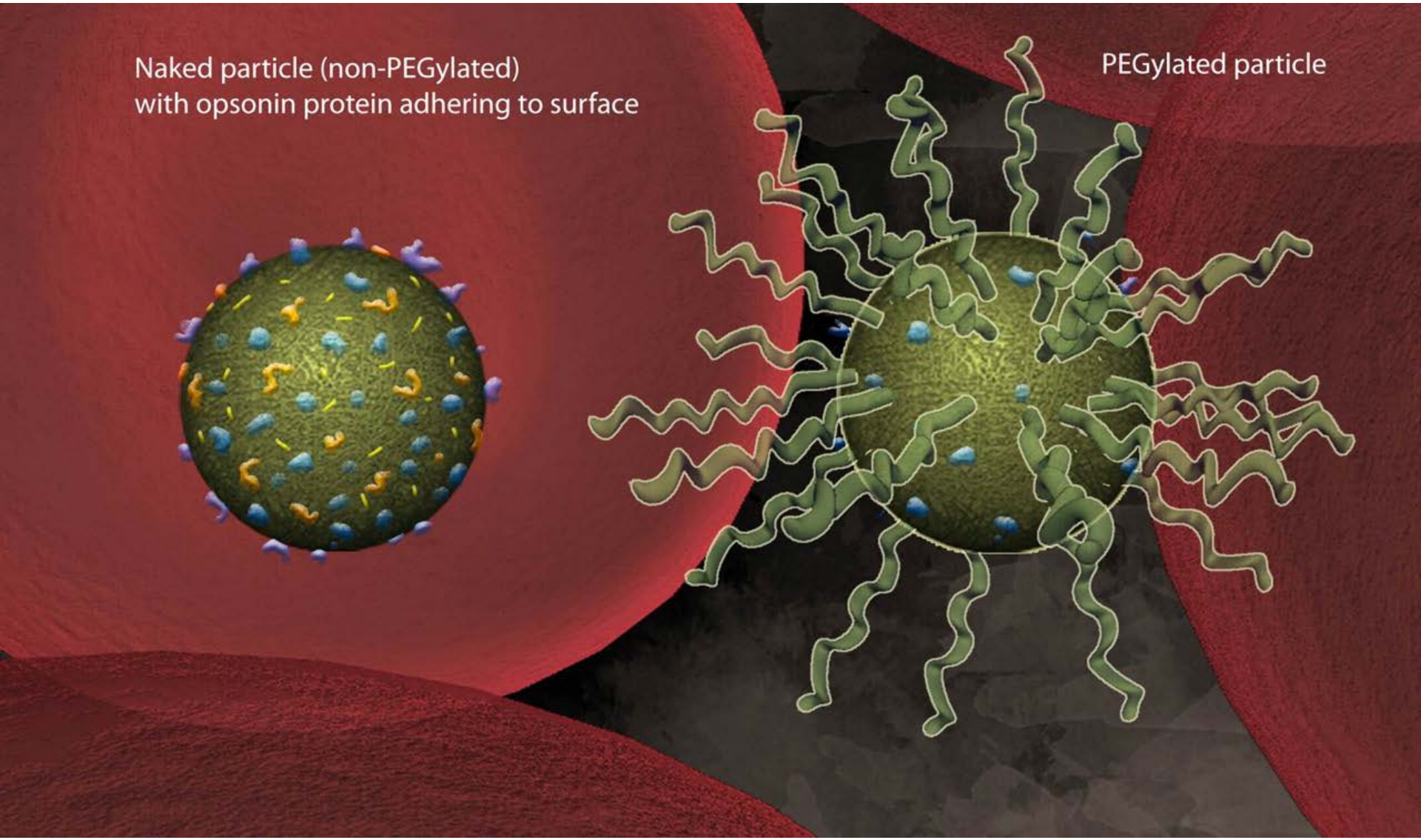


FIGURE 1 | Schematic representation of different strategic designs for nanoparticulate nanomedicines (NNMs). **(A)** Conventional NNM—These NNMs can be modified with charged lipids/polymers, thermosensitive lipids/polymers and/or components for triggered release (e.g., pH-sensitive coating). **(B)** PEGylated NNM—Nanoparticle characteristics and behavior *in vivo* can be modified by the addition of a hydrophilic polymer coating, polyethylene glycol (PEG), to the NNM surface to confer steric stabilization. **(C)** Ligand-targeted NNM—Nanoparticles can be used for active targeting by attaching ligands (e.g., antibodies, peptides and carbohydrates) to its surface or to the terminal end of the attached PEG chains. **(D)** Theranostic NNM – These NNM systems consist of an imaging component and a therapeutic component, and may include a targeting element.

Source: Gert Storm

frontiers in Pharmacology

REVIEW
published: 17 July 2018
doi: 10.3389/fphar.2018.00790


Naked particle (non-PEGylated)
with opsonin protein adhering to surface
PEGylated particle

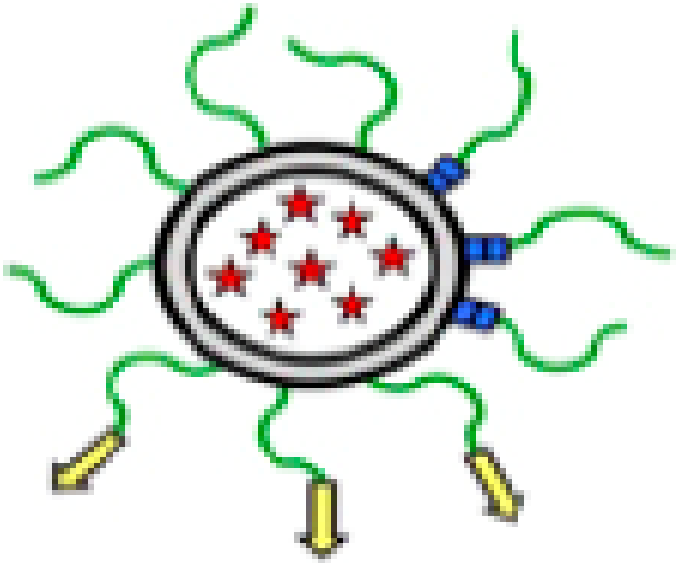
Liposome-Based Nanopharmaceuticals
Doxorubicin

Myocet®

Liposome

Doxil®

PEGylated liposome



Doxorubicin Pharmacokinetics

FORMULATION	Cmax (μM)	Clearance (L*H/M2)	VOL.DISTRIBUTION,ss (L)
MYOCET®	16.0	3.05	34.2
CONVENTIONAL	1.67	27.1	851

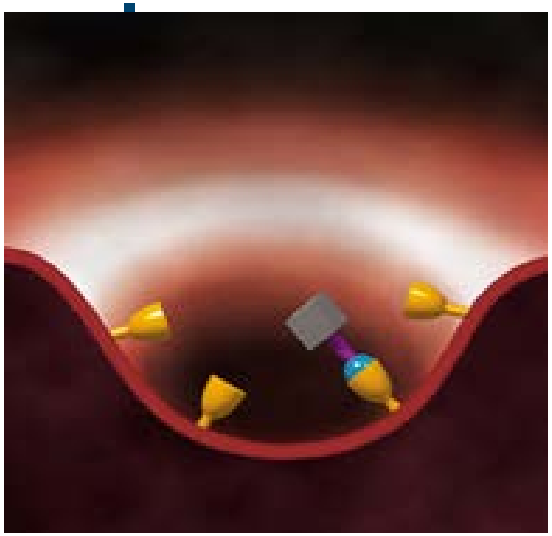
Swenson et al., Anti-Cancer Drugs 14:239-246, 2003

Doxorubicin Clearance (L*hr/M2)

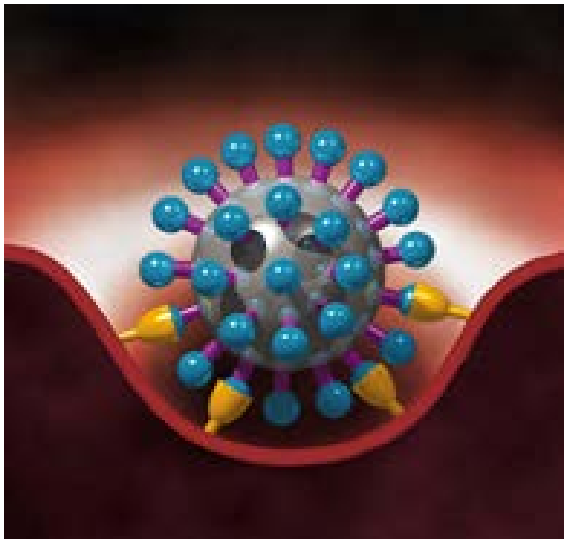
Myocet®	3.05
Doxil®	0.041

Adhesiveness Multivalence

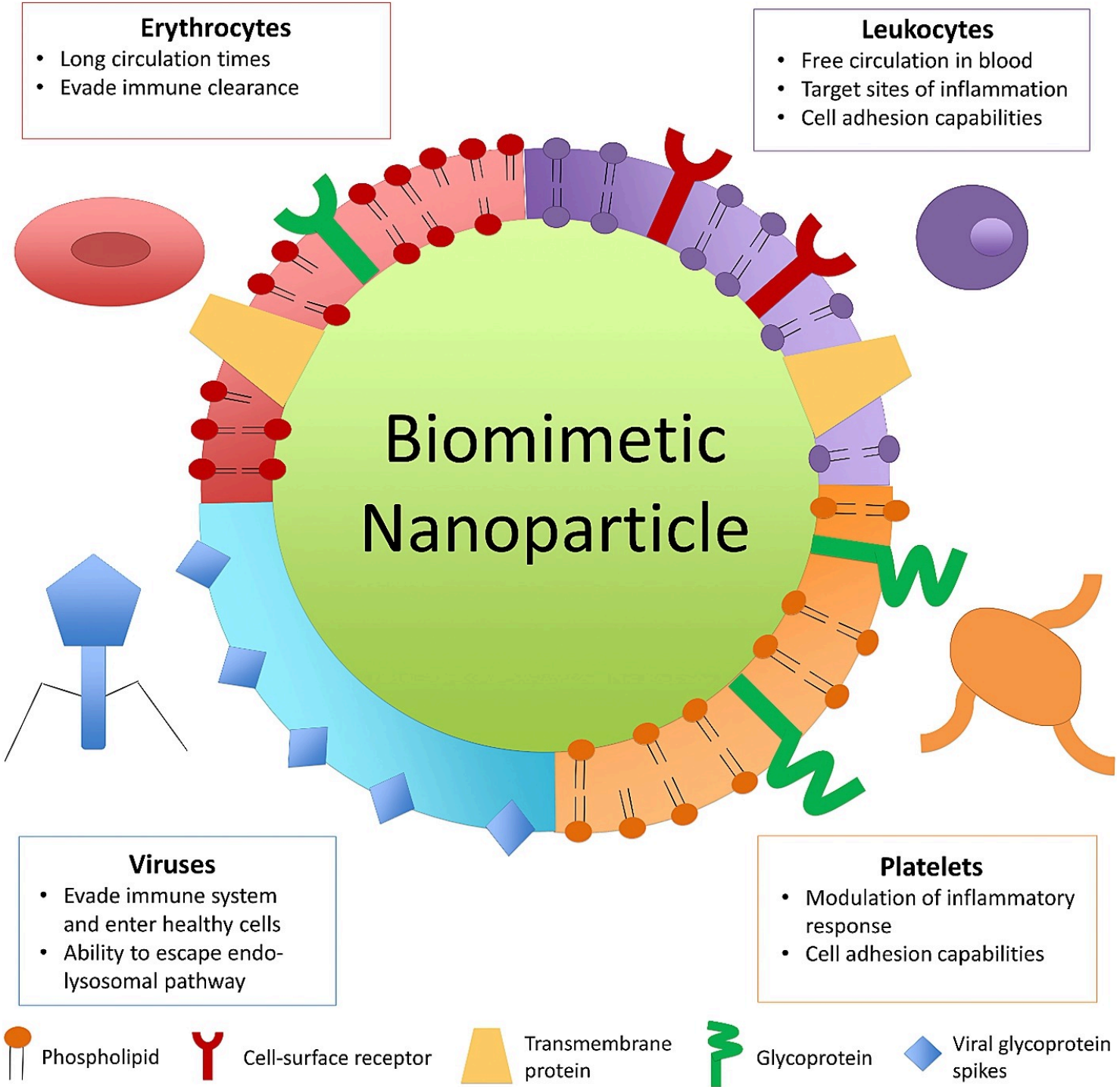
Finally, nanoscale particles have a greater potential for interaction with biological tissues, i.e., an increase in adhesiveness onto biosurfaces. Again, this can be a tricky double-edged issue. On one side, the multiple binding sites of nanodrugs ("multivalence") allow for superior binding to tissue receptors, but on the other side intrinsic toxicity of any given mass of nanoparticles is often greater than that of the same mass of larger particles.



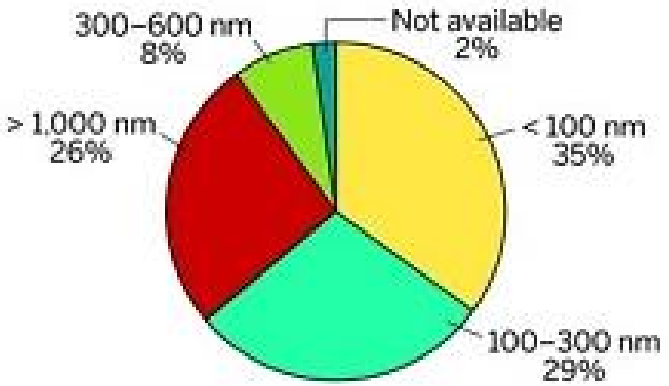
A small molecule will typically interact with only a single receptor on a biological surface.



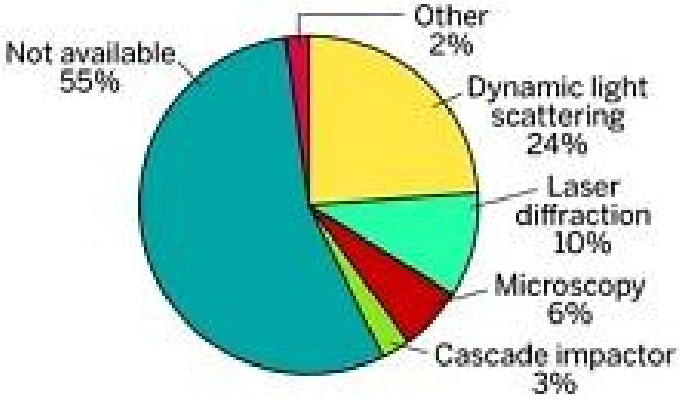
Because of it its size and polyvalent nature, a dendrimer can activate many receptors simultaneously. It can also constrain receptors to remain near each other. Through these mechanisms polyvalency can lead to new or enhanced biological effects.


Erythrocytes
• Long circulation times
• Evade immune clearance
Leukocytes
• Free circulation in blood
• Target sites of inflammation
• Cell adhesion capabilities
Biomimetic Nanoparticle
Viruses
• Evade immune system and enter healthy cells
• Ability to escape endo-lysosomal pathway
Platelets
• Modulation of inflammatory response
• Cell adhesion capabilities
Phospholipid
Cell-surface receptor
Transmembrane protein
Glycoprotein
Viral glycoprotein spikes

PARTICLE SIZE Nanotech drugs in FDA's database have a range of average particle sizes; most are smaller than 300 nm ...



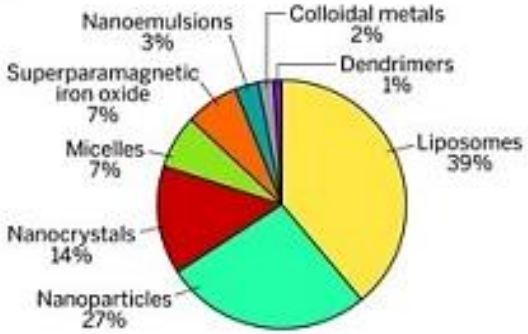
... but most nanotech drugs do not include information about how particle size was measured.



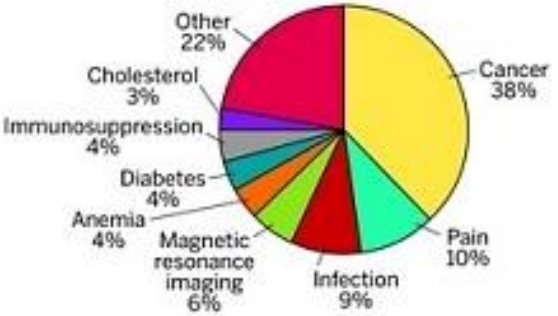
Applications to date = 158

NOTE: There were no applications for drugs with particle sizes between 600 and 1,000 nm. Applications include those for investigational new drugs and new drugs.
SOURCE: FDA

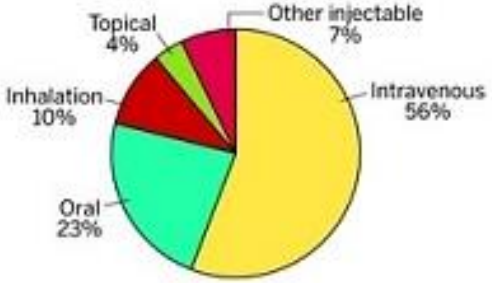
NANODRUGS Liposomes and nanoparticles dominate nanotech-related drug applications submitted to FDA ...



... with the largest class of nanotech-related drugs being developed to fight cancer ...



... and most are developed to be administered intravenously.

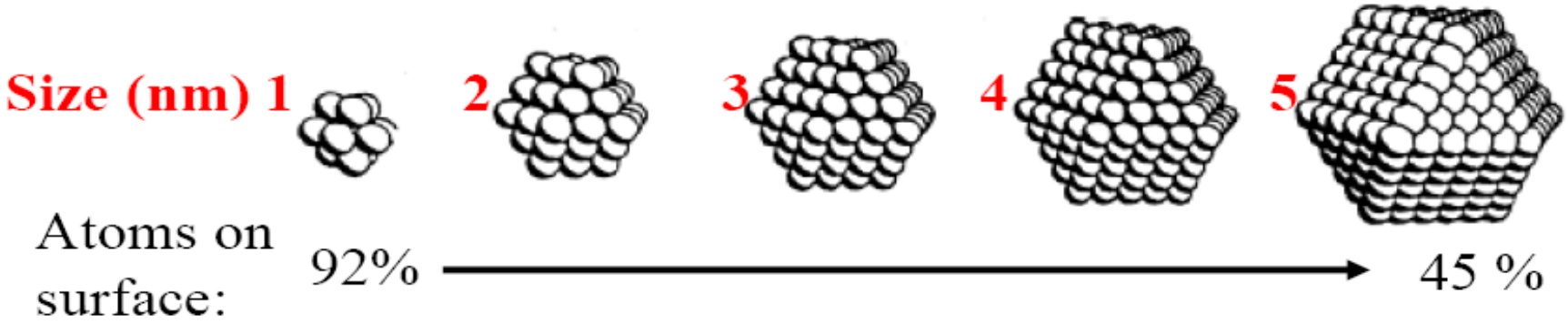


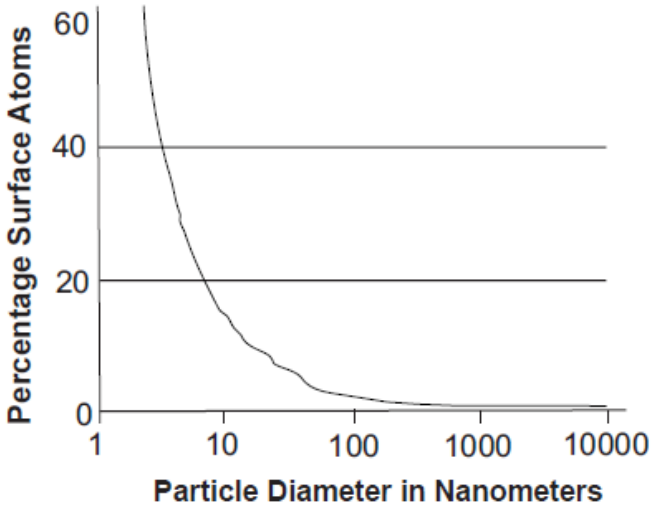
Applications to date = 158

NOTE: Applications include those for investigational new drugs and new drugs. **SOURCE:** FDA

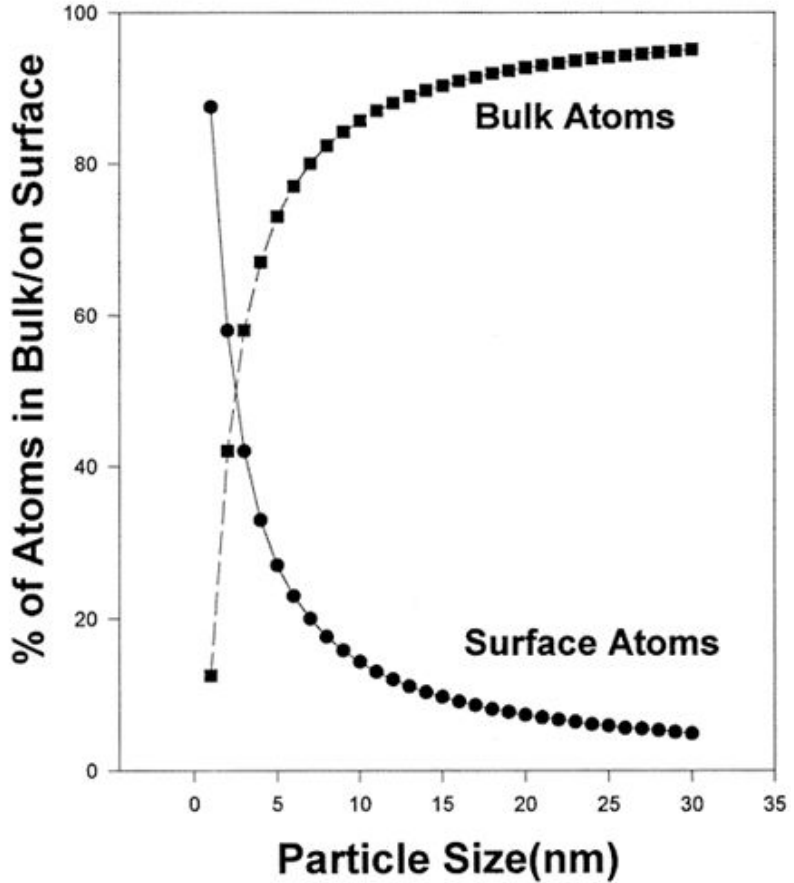
Courtesy: ACS

Size Can Affect Safety





Particle Size Versus Percentage Surface Atoms. As the particle size decreases, the percentage of atoms displayed on the surface of the particle relative to the total atoms in the particle increases exponentially. In other words, the fewer the number of atoms in a particle, a greater percentage of atoms are found on the surface of the particle. In this hypothetical graph, a particle with a 10 nm diameter has ~10–15% atoms displayed on the surface whereas a 50 nm particle has about ~6–8% surface atoms.



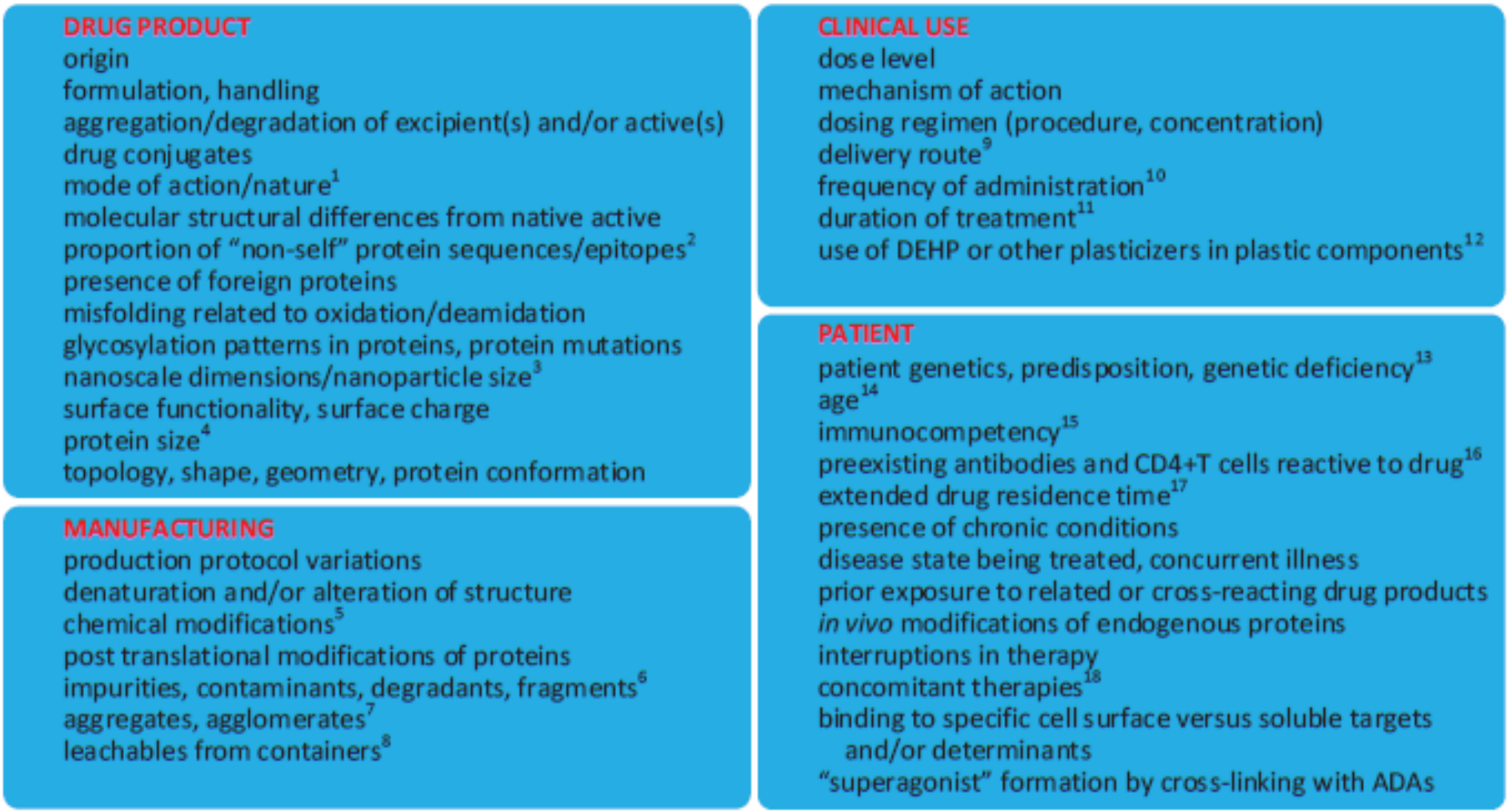


Figure 1.5 Key risk factors contributing to adverse immunogenicity of biologics and nanodrugs. *Abbreviations*: DEHP, di-(2-ethylhexyl) phthalate; ADAs, anti-drug antibodies; CD4+T cell, cluster of differentiation 4 T cell; MHC, major histocompatibility complex.

[1]immunomodulatory versus immunosuppressive, or agonist versus antagonist
[2]proportion of endogenous versus non-endogenous protein sequences; monoclonal antibody-based therapeutics have low immunogenicity
[3]a high surface area to volume ratio when compared to their corresponding bulk counterpart
[4]immunogenicity increases with size
[5]oxidation, deamidation, isomerization has varying effects
[6]host cell proteins, DNA and excipients from formulations are highly immunogenic
[7]unique conformational epitopes may be present
[8]introduction or exposure of new epitopes
[9]immunogenicity order: inhalation > subcutaneous > intraperitoneal > intramuscular > intravenous
[10]repeat administration increases immunogenicity
[11]prolonged exposure increases immunogenicity
[12]di(2-ethylhexyl) phthalate (DEHP) is a manufactured chemical that is commonly added to plastics to make them flexible
[13]certain MHC alleles, polymorphisms in cytokine genes, autoimmune or proinflammatory predisposition has a higher immunogenicity risk
[14]pediatric versus adult immune system
[15]if the patient is immunosuppressed, then may be more immunotolerant
[16]examples include cross-reacting auto-antibodies, preexisting anti-PEG antibodies
[17]at a specific site of action, within specific targeted tissue or in systemic circulation
[18]co-medicated immunosuppressive drugs (e.g., methotrexate or steroids) reduce immunogenicity

Figure 1.5 Key risk factors contributing to adverse immunogenicity of biologics and nanodrugs. *Abbreviations*: DEHP, di-(2-ethylhexyl) phthalate; ADAs, anti-drug antibodies; CD4+T cell, cluster of differentiation 4 T cell; MHC, major histocompatibility complex.

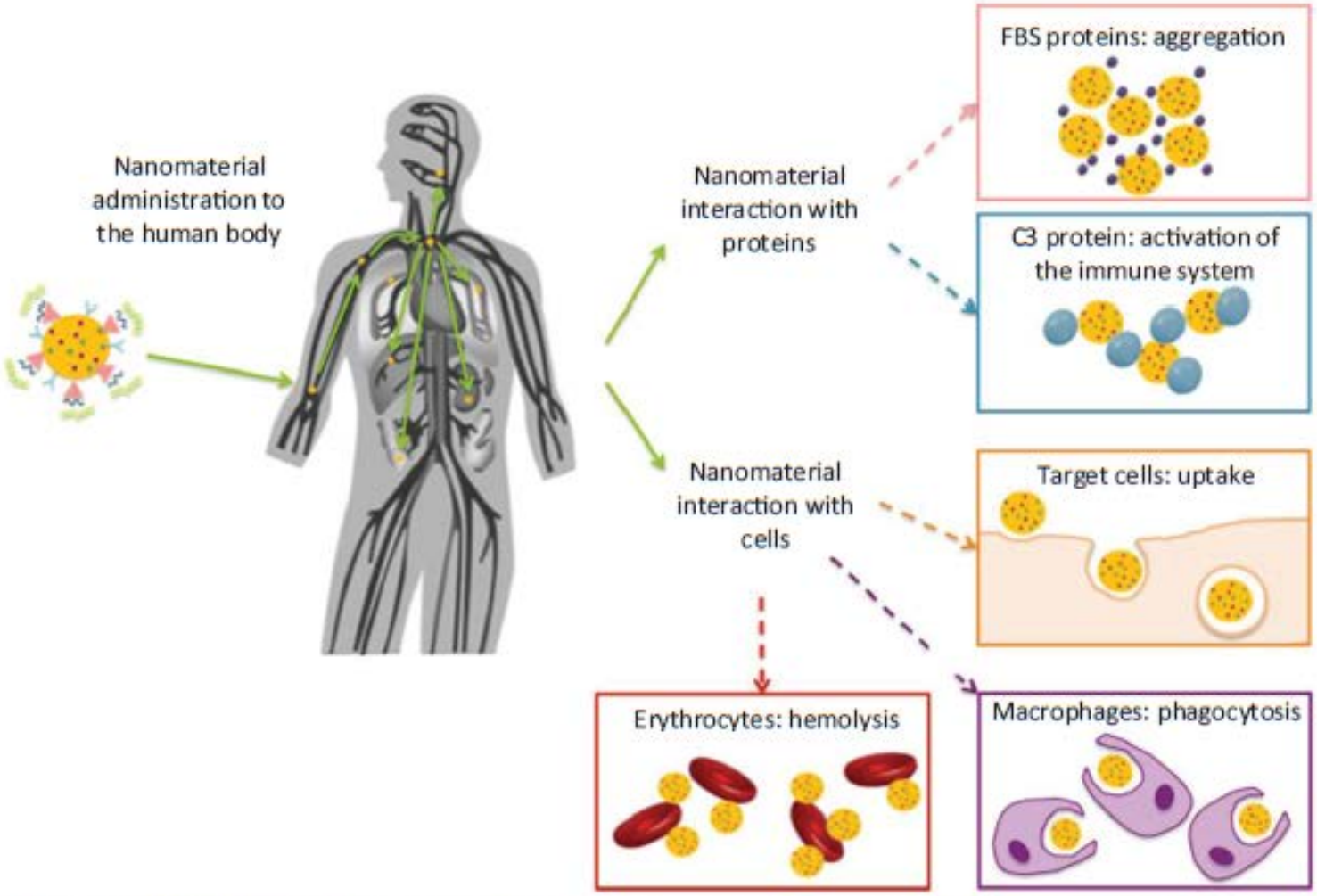
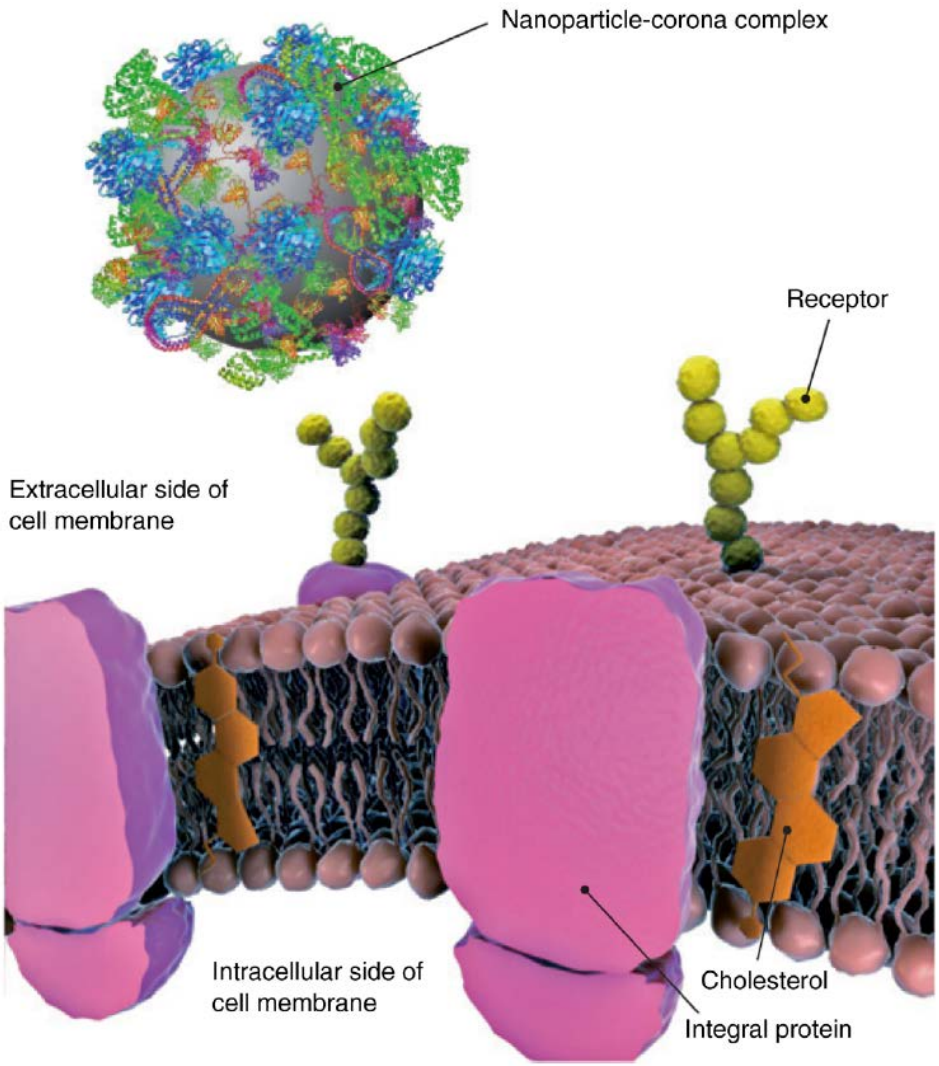


Figure 1.8 Schematic representation of possible interactions of some nanosystems with biological components, namely cells and proteins. Courtesy of Dr. Cristina Fornaguera, Sagetis-Biotech, Barcelona, Spain.

The Nanoparticle Corona as an Immunological Barrier



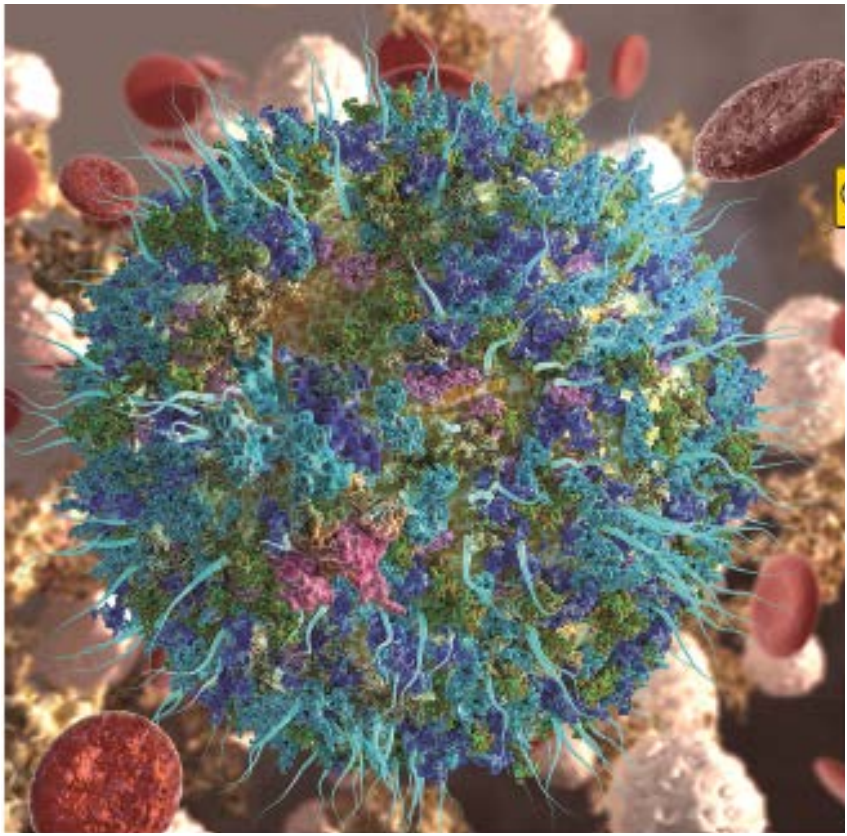
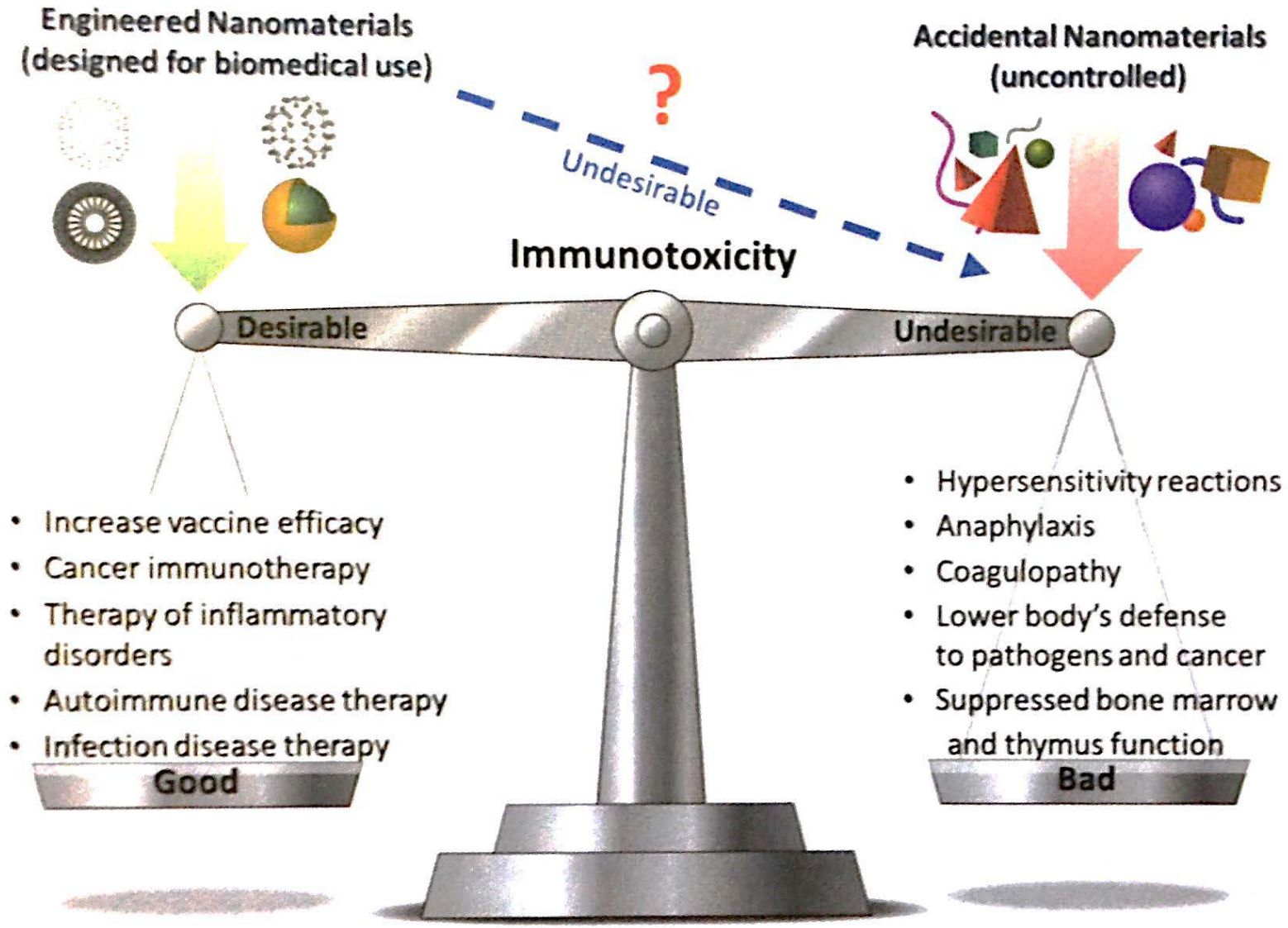


Figure 2.6 It is the NP–corona complex, rather than the bare NP, that interacts with biological machinery, here with a cell membrane receptor. (Reprinted with permission from Ref. [54], © 2012 Elsevier B.V.)

Source: Lademann, J. *et al.* (2013) Drug delivery with topically applied nanoparticles: science fiction or reality. *Skin Pharmacol. Physiol.*, **26** (4–6), 227–233.



Source: Dr. S. McNeil

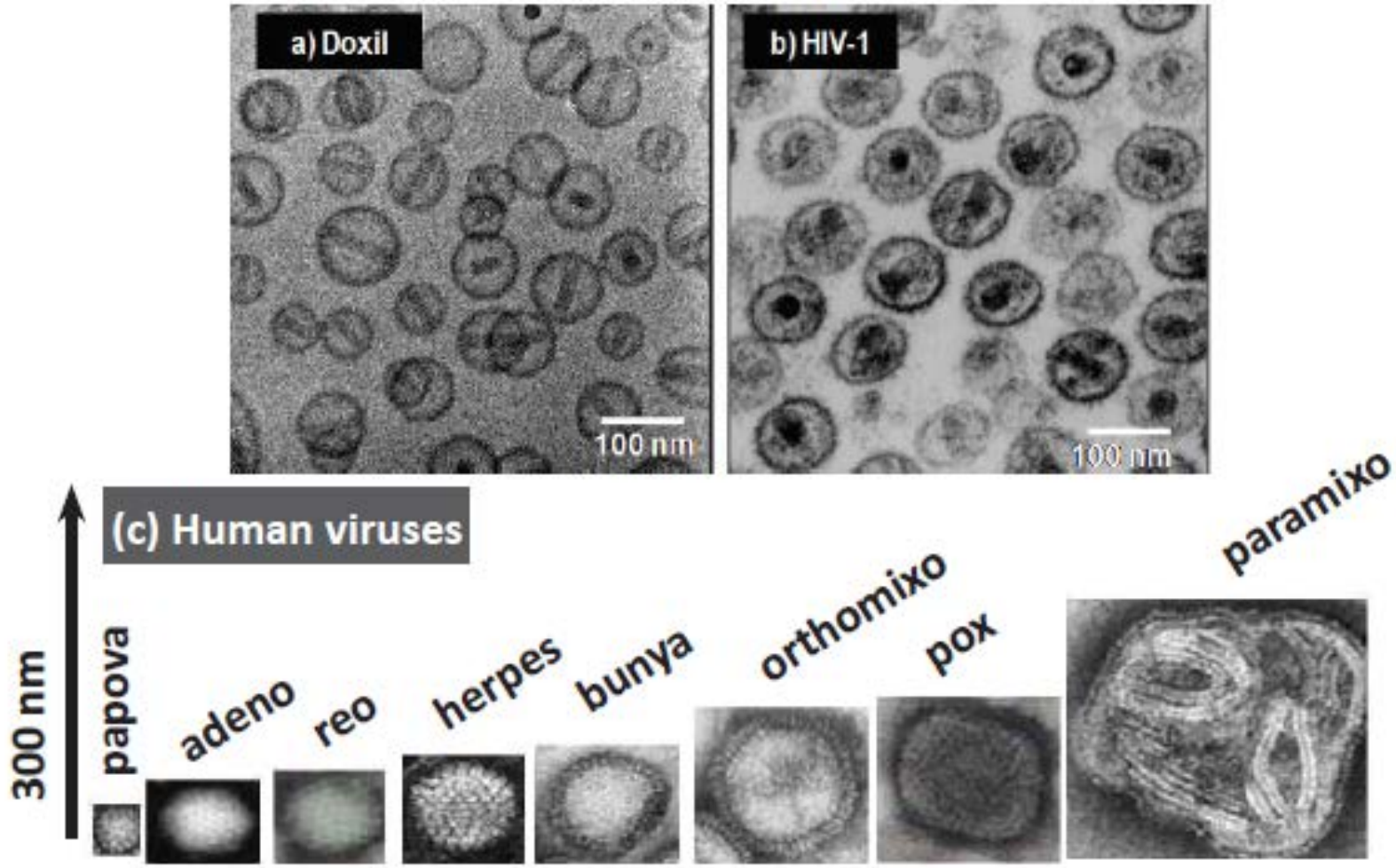


Figure 2.5 Size range of pathogenic virus strains in the 40–300 nm range.

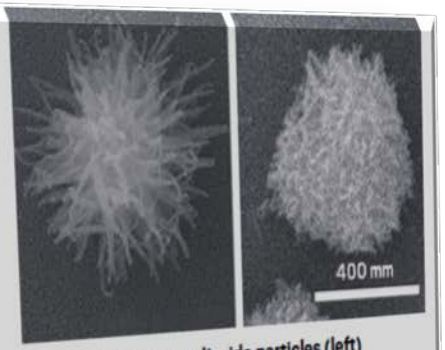
Immunological Issues with Medicines of Nano Size: The Price of Dimension Paradox[1]

János Szebeni, MD, PhD, DSc,[a,b,c] and Raj Bawa, MS, PhD[d,e,f]

NANOMATERIALS

Particles provoke immune response

A dose of spiky particles improves the efficacy of cancer treatment and flu vaccine in animals



Spiky titanium dioxide particles (left) provoke a bigger immune response than rough ones (right).

Vaccines and cancer immunotherapies work by activating the immune system with biochemical signals. A new study shows that the immune system can also respond to physical cues such as the texture of injected nanoparticles, potentially opening up new ways to design therapies for cancer and other diseases.

Many pathogens, including the flu virus, have spikelike features on their surface, and scientists have wondered whether their characteristic shapes have a role in triggering the immune system. To test whether physical cues could help activate an immune response, Mei X. Wu of Massachusetts General Hospital and Xi Xie of Sun Yat-Sen University designed an experiment that allowed them to isolate shape-based and biochemical cues.

First, they made two sets of nanoparticles from titanium dioxide, a compound that doesn't usually trigger the immune system. Some were spiky, some rough. They coated some of them with a lipid found on the surface of some bacterial cells to act as an immune irritant. Then they injected mice with the particles along with a cancer therapy and a flu vaccine. The lipid-coated spiky particles amplified immune responses and boosted the efficacy of the cancer immunotherapy and the flu vaccine. Coated rough particles had no significant effect (*Nat. Nanotech.* 2018, DOI:10.1038/s41565-018-0274-0).

Cells dosed with spiky particles showed evidence of mechanical stress on their membranes, and activation of a signaling pathway known to play a critical role in response to immunotherapies. Researchers suspect that the spikes stress the cell membrane, causing potassium channels in the cells to open and ultimately activating the pathway.

Wu says researchers designing immunotherapies should take advantage of these effects. Therapies combining physical and biochemical cues could produce robust responses. And they could be approved quickly because the materials used in this study are already in medical use, says John Hayball of the University of South Australia.

Brandon M. Johnson of University of North Carolina, Chapel Hill, who wrote a perspective article about the study (*Nat. Nanotech.* 2018, DOI:10.1038/s41565-018-0292-y), says he'd like to see if the stiffness of the spikes makes a difference and whether other, less rigid materials could achieve similar effects.—CICI ZHANG

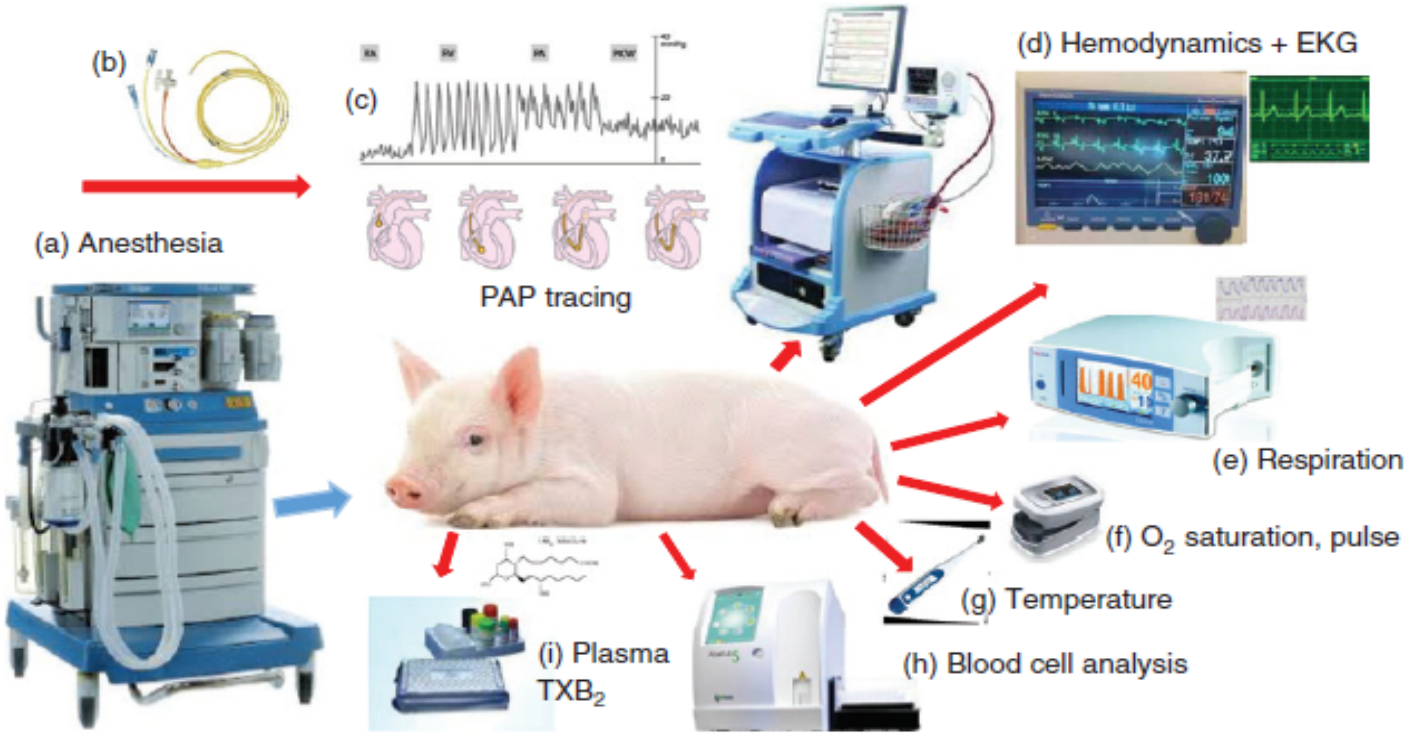
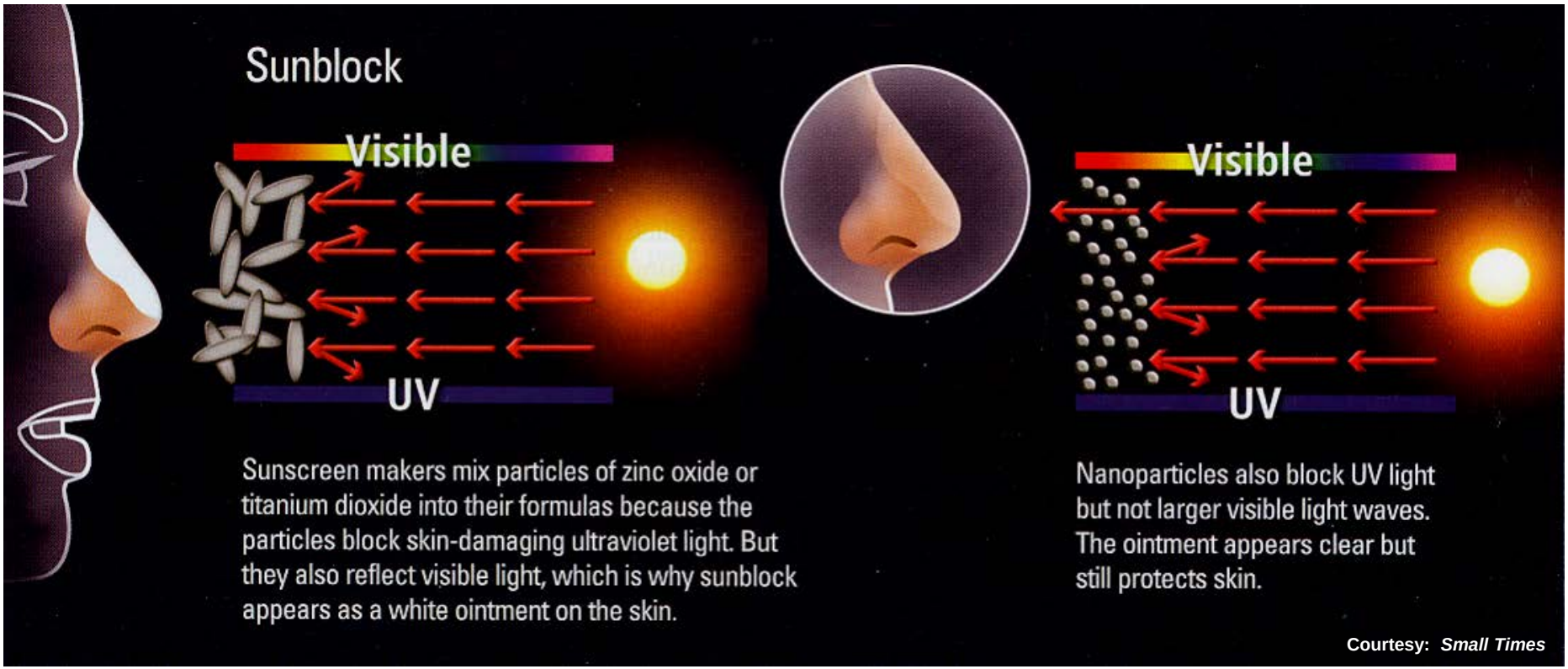


Figure 2.7 Parameters measured and equipment used in the porcine CARPA model: (a) Anesthesia machine; (b) Swan–Ganz balloon catheter, used for the measurement of pulmonary arterial pressure; (c) blood pressure wave forms during passage of the tip of the Swan–Ganz catheter via the right atrium, right ventricle, and pulmonary artery until being wedged into the pulmonary capillary bed; (d) computerized hemodynamic monitoring system tracing the systemic and pulmonary pressures, heart rate, and the EKG; (e) capnograph measuring the respiratory rate (RR) and end-tidal carbon dioxide ($EtCO_2$); (f) pulse oximeter measuring oxygen saturation and pulse rate; (g) rectal temperature probe; (h) blood cell analyzer; and (i) enzyme linked immunosorbent assay for measuring plasma mediators, such as TxB2. Reprinted with permission from [36].

Source: Janos Szebeni, MD

It is likely that certain marketed nanoproducts like cosmetics which are not subject to pre-market approval (e.g., sunscreens containing zinc oxide and titanium dioxide) warrant some sort of safety labeling to alert the unsuspecting consumer.

Are most nanomaterials used in nanoproducts inherently toxic?



THE GREAT BIG QUESTION

ABOUT REALLY TINY MATERIALS

Current Drug Delivery, 2011, *8*, 227-234

Regulating Nanomedicine – Can the FDA Handle It?

Raj Bawa*,#

"There's no need right now to issue guidance documents specifically for nanomaterials The existing framework can accommodate the kind of nanoparticle therapeutics under development. We're viewing nanoparticle-containing drugs as just new drugs."

G. K. Shaw. (2010). FDA Process For Nano Drug Review "Adequate," Official Says. New Haven Independent. October 15, 2010.

41

FDA and Nanotech: Baby Steps Lead to Regulatory Uncertainty

Raj Bawa

Bawa Biotech LLC, Ashburn, VA, USA and Rensselaer Polytechnic Institute, Troy, NY, USA

Bio-Nanotechnology: A Revolution in Food, Biomedical and Health Sciences, First Edition. Edited by Debasis Bagchi, Manashi Bagchi, Hiroyoshi Moriyama, and Fereidoon Shahidi.

US FDA + Baby Steps = Regulatory Uncertainty?

- If the sponsor or manufacturer makes “nano” claims regarding the manufacture or performance of the product, FDA may be unaware that the product being reviewed and in the approval process employs nanotech or contains nanomaterials.
- European Medicines Agency?

CHAPTER 12

The Challenge of Regulating Nanomedicine: Key Issues

RAJ BAWA,*[a,b] YECHEZKEL BARENHOLZ[c] AND ANDREW OWEN[d]

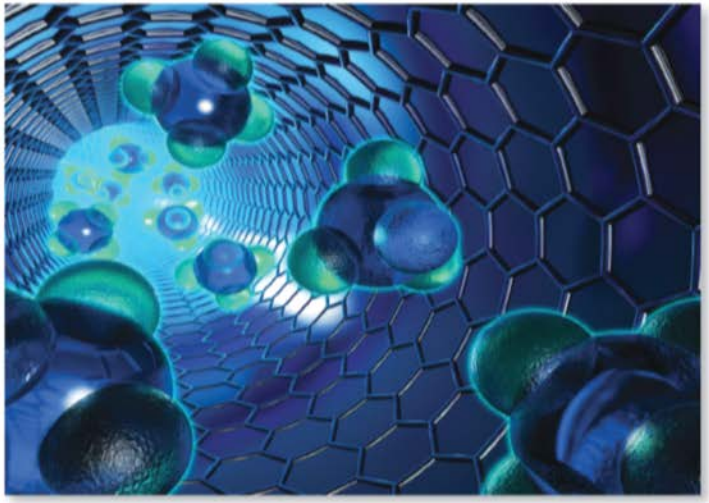
[a] Patent Law Department, Bawa Biotech LLC, Ashburn, Virginia, USA; [b] Department of Biological Sciences, Rensselaer Polytechnic Institute, Troy, New York, USA; [c] Laboratory of Membrane and Liposome Research, Department of Biochemistry and Molecular Biology, Institute for Medical Research Israel – Canada (IMRIC), The Hebrew University-Hadassah Medical School, Jerusalem, Israel; [d] Department of Molecular and Clinical Pharmacology, University of Liverpool, UK
*Email: bawa@bawabiotech.com

RSC Drug Discovery Series No. 51
Nanomedicines: Design, Delivery and Detection
Edited by Martin Braddock

Published by the Royal Society of Chemistry, www.rsc.org

The New York Academy of Sciences

Presents



Nanomedicines:
Addressing the Scientific and Regulatory Gap

NOVEMBER 21, 2013

www.nyas.org/NanoMed

The New York Academy of Sciences, New York City

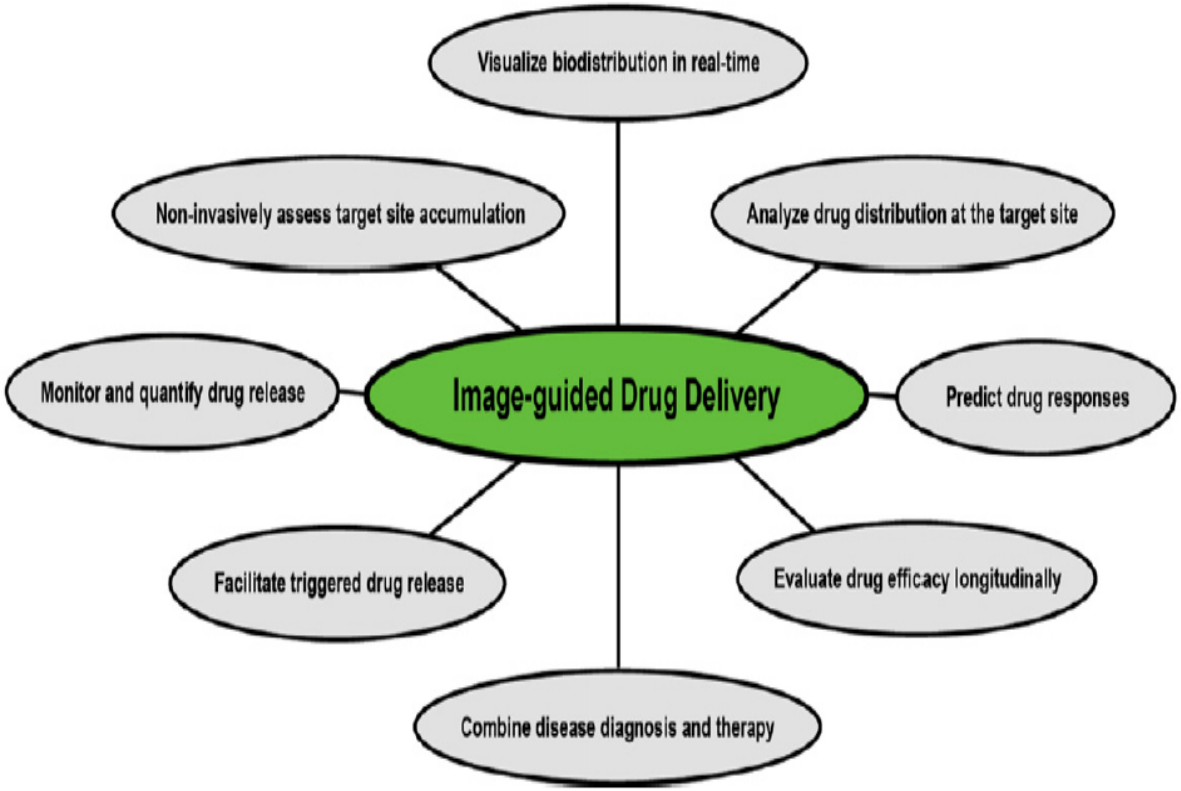
New Drug Application (NDA) or Abbreviated New drug Application (ANDA)?

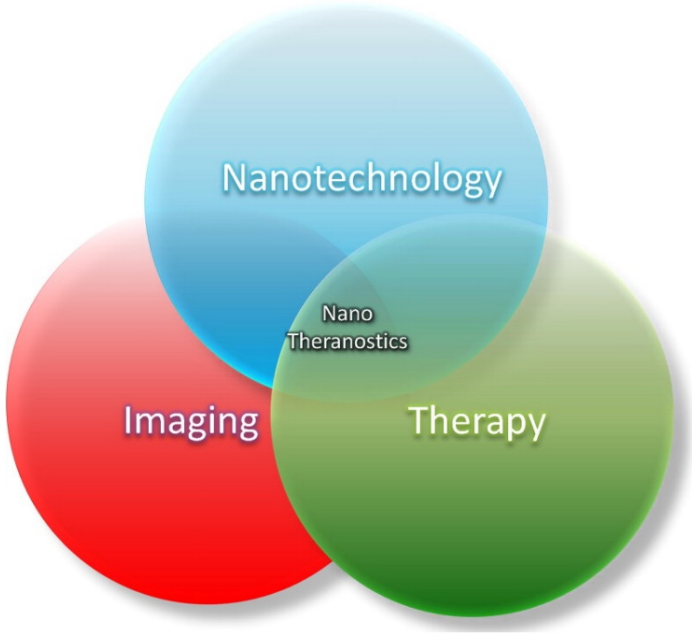
Pharmacokinetic parameters of 10 mg/kg dose administration paclitaxel formulated in the TPGS-emulsified PLGA NPs *versus* Taxol®.

	Taxol® (i.v.)	Taxol® (oral)	TPGS NPs (oral)
C_{max} (ng/mL)	33,100	103.6	459
$AUC_{(0-t)}$ (ng h/mL)	35,500	872	8510
Sustainable time (h)	21.2	7.02	88.2
Bioavailability (%)		2.46%	24.0%

Lin Mei et al. Pharmaceutical nanotechnology for oral delivery of anticancer drugs. Advanced Drug Delivery Reviews Volume 65, Issue 6, 2013, pages 880 – 890.

The Coming Age of Theranostics





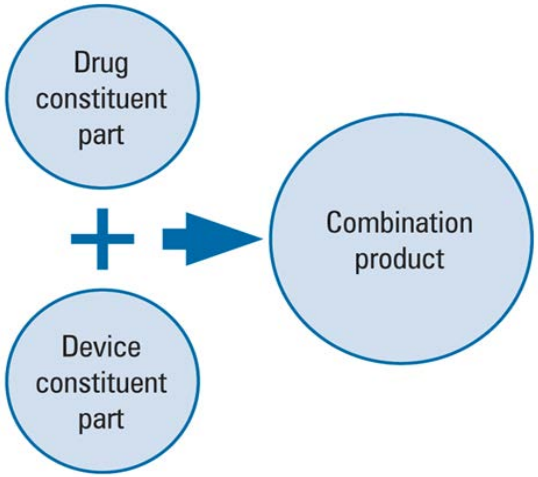
Theranostics allows for the imaging of cells before, during, and after treatment with a drug, thus providing a level of detection and assessment that is not currently available in cancer chemotherapy.

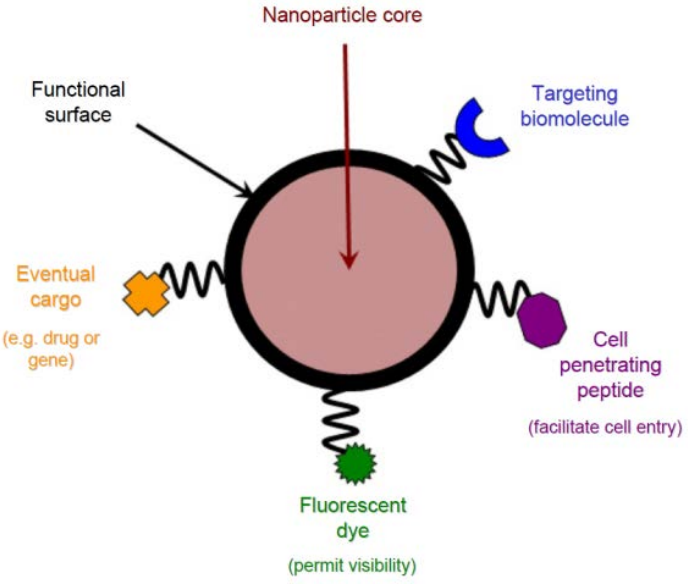
Leading the way in this new form of *personalized medicine* are NPs which, when equipped with imaging agents, drugs and targeting groups, can in principle report the results of treatment at the cellular level.

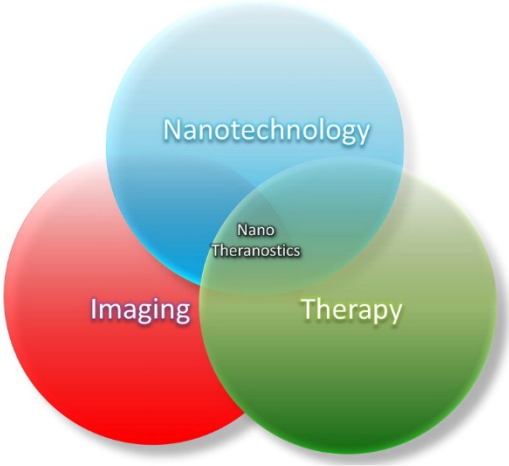
Are Most Nanoproducts combination products?

- FDA category-based system involving the “primary mode of action (PMOA)” improper in certain cases?
- Classification process at the FDA is frequently imprecise as it is not always possible to clearly elucidate a combination product’s PMOA.
- The coming age of theranostics

(Image-Guided DD)





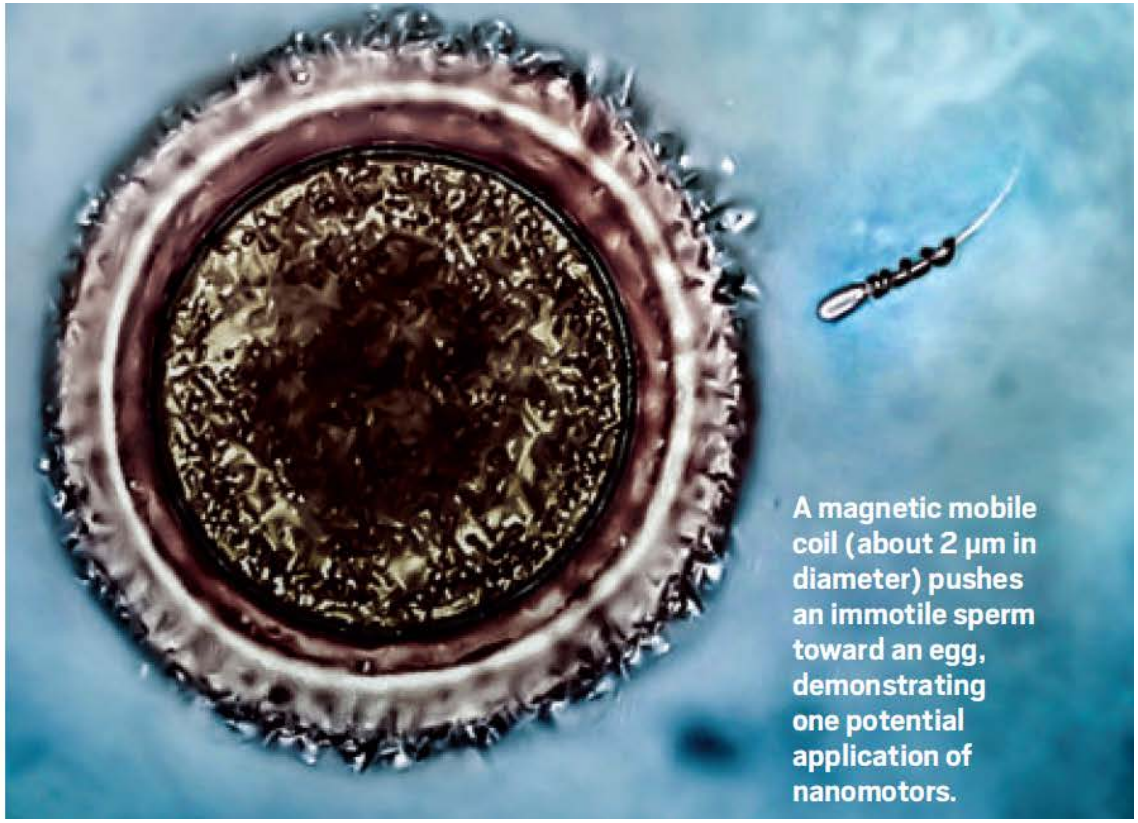


Regulating Nanomotors

ACS MEETING NEWS

Steering nanomotors toward applications

Tiny machines are revved up to leave the lab, but they face roadblocks

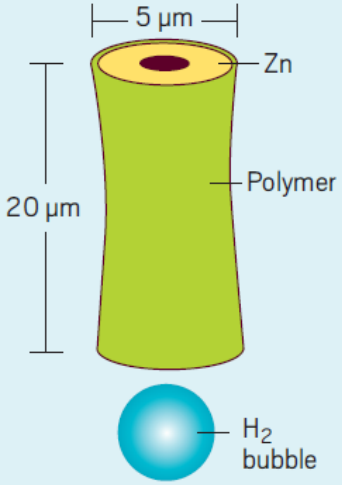


A magnetic mobile coil (about 2 μm in diameter) pushes an immotile sperm toward an egg, demonstrating one potential application of nanomotors.

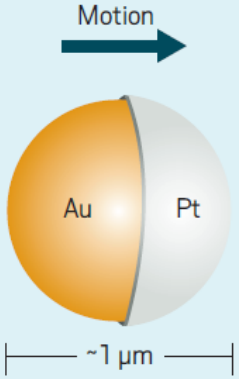
Nanomotorin'

An illustrative but incomplete guide to propulsion methods and motors

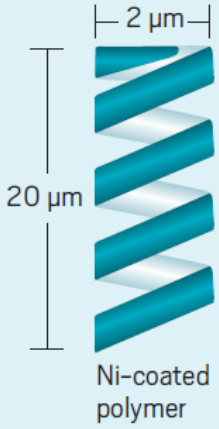
What makes it go?
Bubbles
How does it work?
Materials in a motor react with chemical fuel in its environment to generate gas bubbles that send the motor swimming like a torpedo.
Where has it gone lately?
Zinc-filled microcylinders torpedoed themselves into the stomach tissue of mice, thanks to hydrogen bubbles that evolve when the metal reacted with stomach acid.[a]



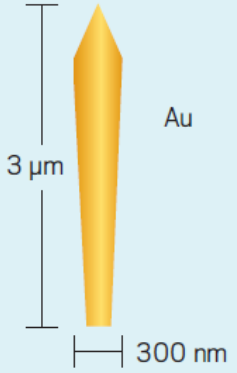
What makes it go?
Self-electrophoresis
How does it work?
Rods or spheres made from multiple metals create chemical concentration gradients thanks to their asymmetric catalytic properties. The gradients create local electric fields that propel the motors.
Where has it gone lately?
Janus particles made from gold and platinum propelled themselves into cracks in circuits to repair electronics.[b]



What makes it go?
Magnetic fields
How does it work?
Researchers can steer particles made using magnetic metals with magnetic fields.
Where has it gone lately?
Researchers mobilized immotile but otherwise healthy sperm with the help of magnetic microhelices.[c]

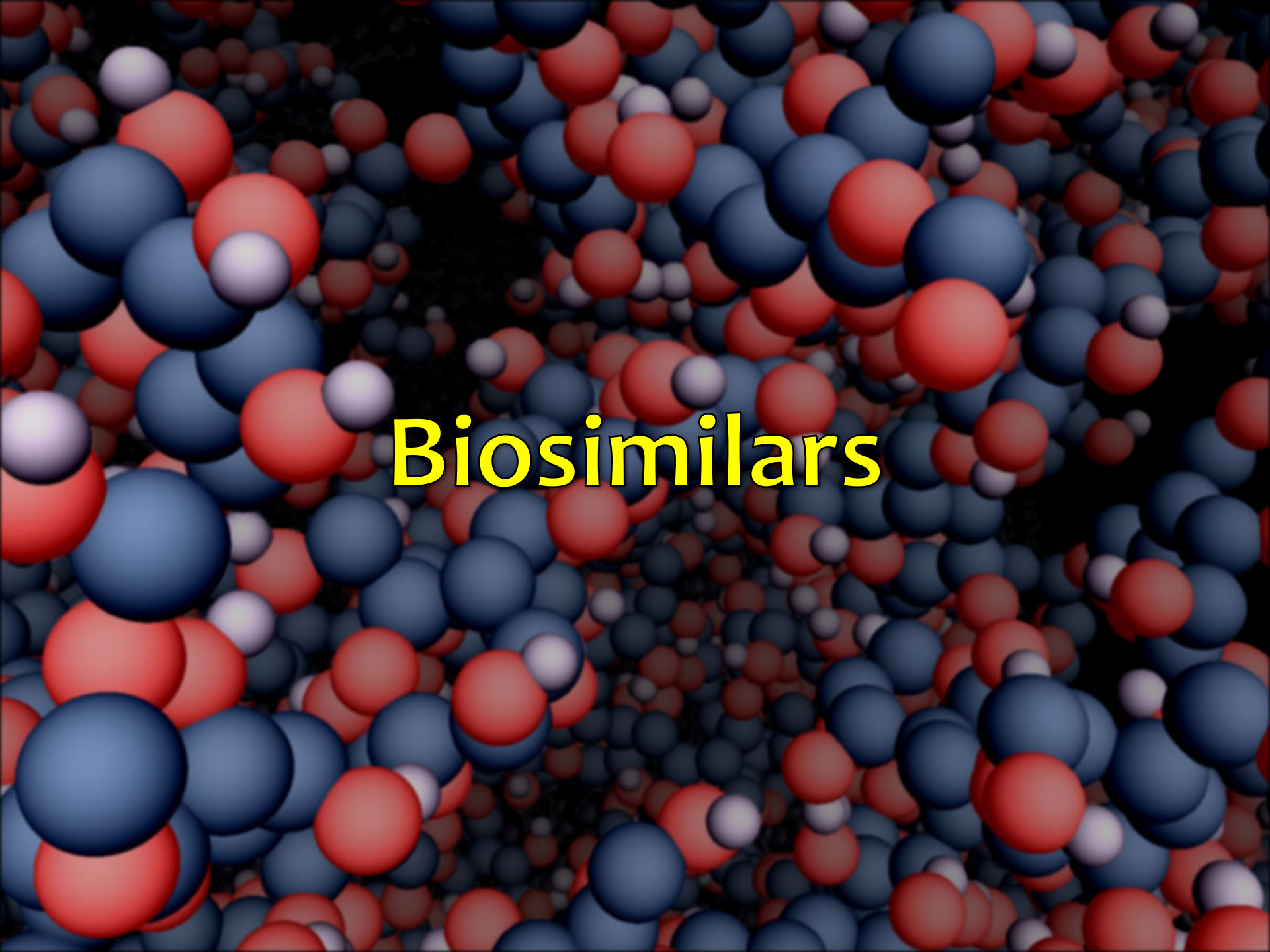


What makes it go?
Acoustic energy
How does it work?
Waves generated by ultrasound can drive asymmetrically shaped particles.
Where has it gone lately?
Ultrasound allowed researchers to drive gold nanomotors around inside cells for the first time in 2014.[d]



Note: Dimensions shown are specific to application described. **a** *ACS Nano* 2015, DOI: 10.1021/nn507097k. **b** *Nano Lett.* 2015, DOI: 10.1021/acs.nanolett.5b03140. **c** *Nano Lett.* 2016, DOI: 10.1021/acs.nanolett.5b04221. **d** *Angew. Chem. Int. Ed.* 2014, DOI: 10.1002/anie.201309629. **Source**: Adapted from the Wang group and C&EN

Regulating Nano-factories for Personalized Drugs


Biosimilars

Enter Biosimilars, Nanosimilars, NBCD Similars

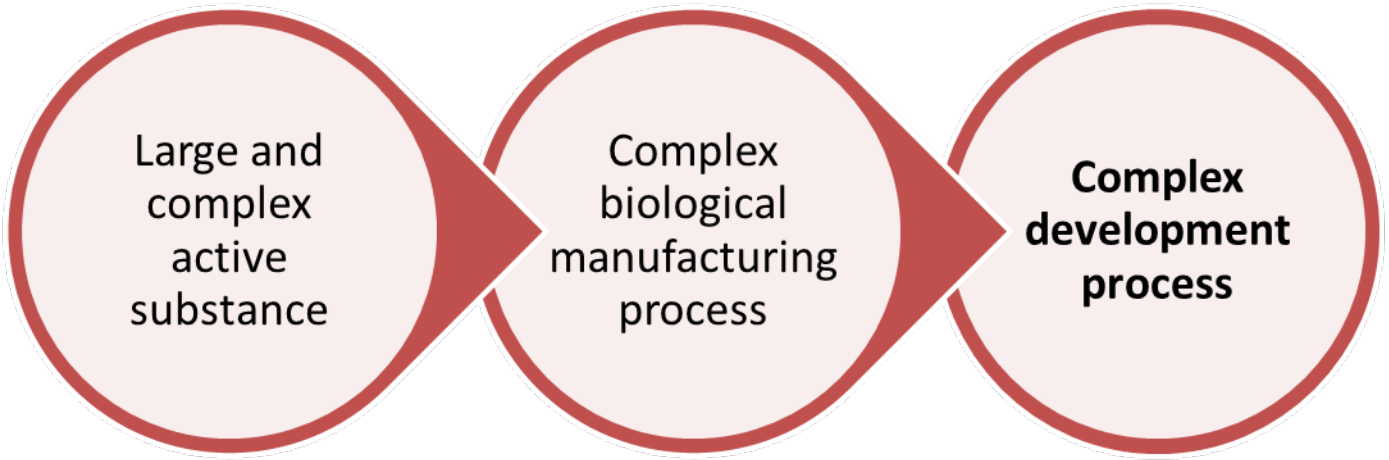
Table 1.2 FDA regulatory routes for therapeutic products

	Medical Devices	Drugs	Biologics
FDA Center Jurisdiction	CDRH	CDER	CBER/CDER
Regulatory Route(s)	510(k) waived 510(k) notification PMA	OTC ANDA NDA	BLA
Clinical Trial Initiation	IDE	IND	IND

Abbreviations: CBER, Center for Biologics Evaluation and Research; CDER, Center for Drug Evaluation and Research; CDRH, Center for Devices and Radiological Health; NDA, New Drug Application; BLA, Biologic License Application; OTC, over-the-counter; ANDA, Abbreviated New Drug Application; PMA, Premarket Approval Application; IND, Investigational New Drug; IDE, Investigational Device Exemption.

Biosimilars

A biosimilar is a product that is **physically**, **chemically**, **biologically**, and **clinically similar** to an approved reference **biological product.**



THE NEED FOR U.S. BIOSIMILARS

EXPRESS SCRIPTS®

Generic drugs were introduced 30 years ago, saving billions of dollars, improving patient access and changing healthcare forever. Biosimilars now hold the same potential.

U.S. SPECIALTY Rx SPEND

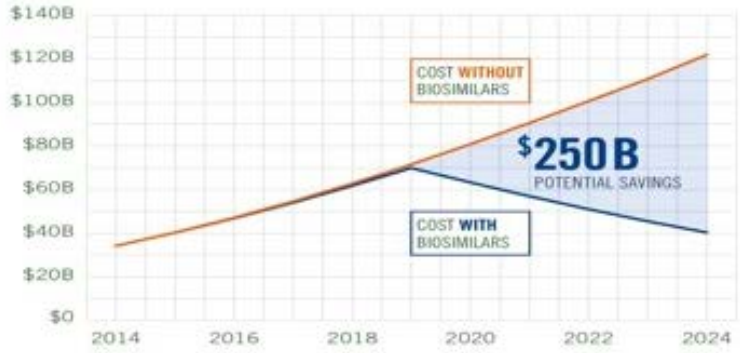
4X SINCE 2006

BY 2018, SPECIALTY DRUGS WILL ACCOUNT FOR:

1% OF ALL U.S. PRESCRIPTIONS

50% OF ALL Rx COST

$250 BILLION COULD BE SAVED IN THE NEXT DECADE IF THESE 11 BIOSIMILARS ARE APPROVED



- Avastin® *(bevacizumab)*
- Epogen® *(epoetin alfa)*
- Herceptin® *(trastuzumab)*
- Humira® *(adalimumab)*
- Intron A® *(interferon alfa-2a)*
- Neulasta® *(pegfilgrastim)*
- Neupogen® *(filgrastim)**
- Pegintron® *(peginterferon alfa-2b)*
- Procrit® *(epoetin alfa)*
- Remicade® *(infliximab)**
- Rituxan® *(rituximab)*

*Awaiting FDA approval.

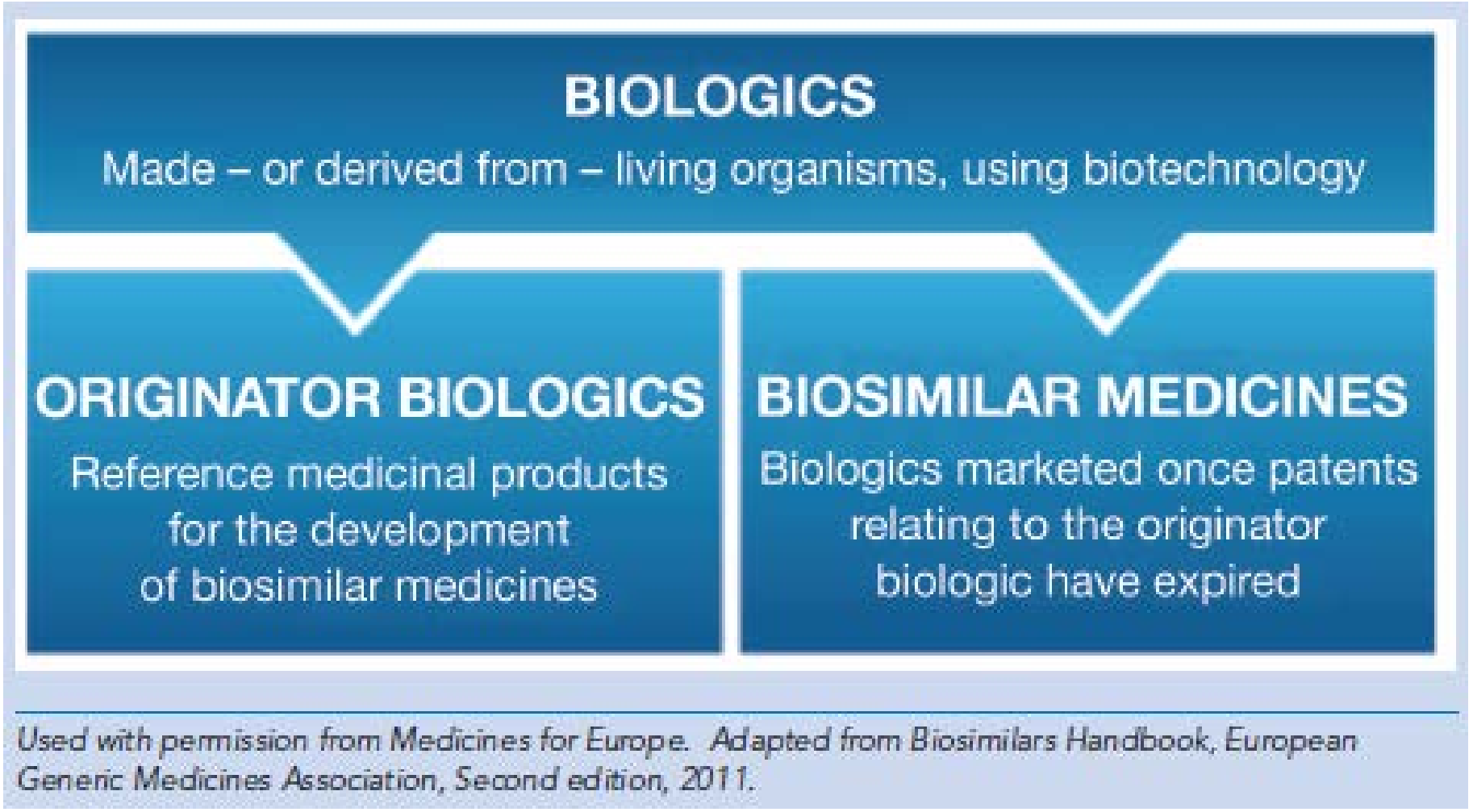
WE KNOW
BIOSIMILARS CAN DRIVE COST DOWN SAFELY

Biosimilars have been lowering healthcare costs around the globe **since 2006 with no related safety issues.**

WE NEED
A CLEAR PATH FORWARD IN THE U.S.

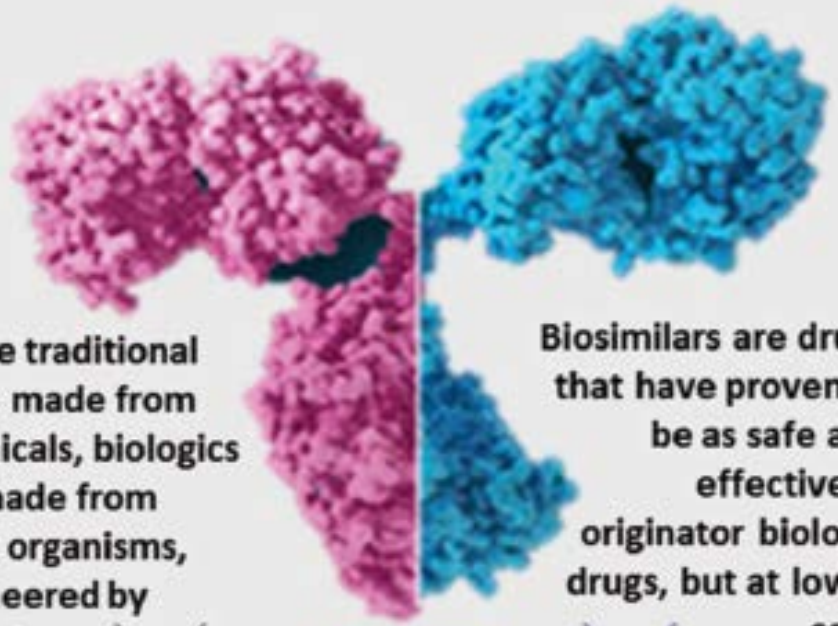
- FDA APPROVAL
- NO UNNECESSARY HURDLES IN STATE SUBSTITUTION LAWS
- EASY-TO-USE NAMING STRUCTURE

For the latest Express Scripts research, visit: http://Lab.Express-Scripts.com.



Used with permission from Medicines for Europe. Adapted from Biosimilars Handbook, European Generic Medicines Association, Second edition, 2011.

BIOLOGICS VS. BIOSIMILARS



Unlike traditional drugs made from chemicals, biologics are made from living organisms, engineered by scientists.

Biosimilars are drugs that have proven to be as safe and effective as originator biologic drugs, but at lower cost.

Biologics can cost up to $100,000 annually.

Biosimilars are estimated to cost 20-30% less than the originator biologic.

Figure 14.1 Global Biosimilars Market Forecast: Distribution by Region, 2020 and 2025 (USD Billion)

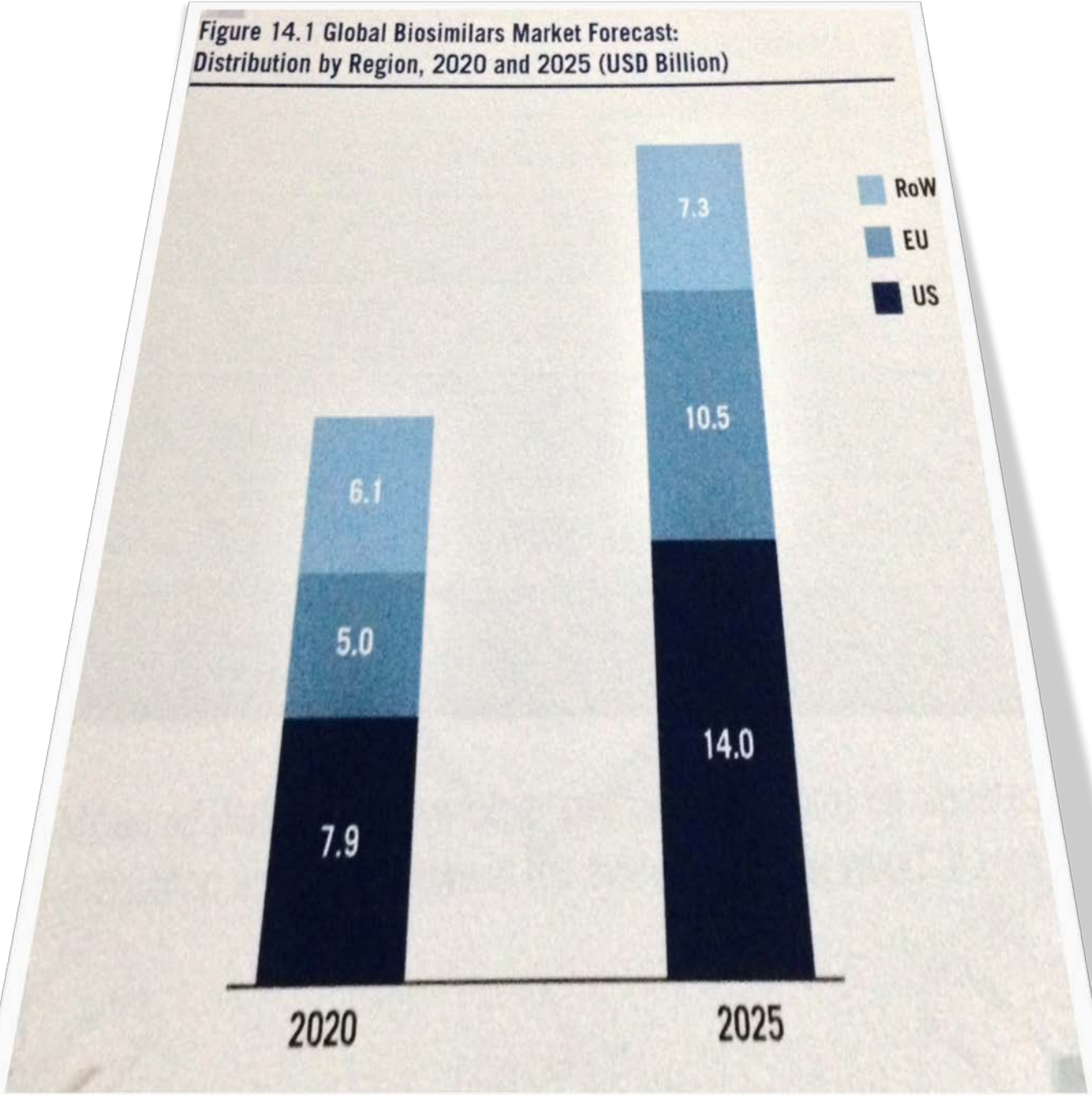


Figure 14.2 Global Biosimilars Market Forecast: Distribution by Product Category, 2020 and 2025 (USD Billion)

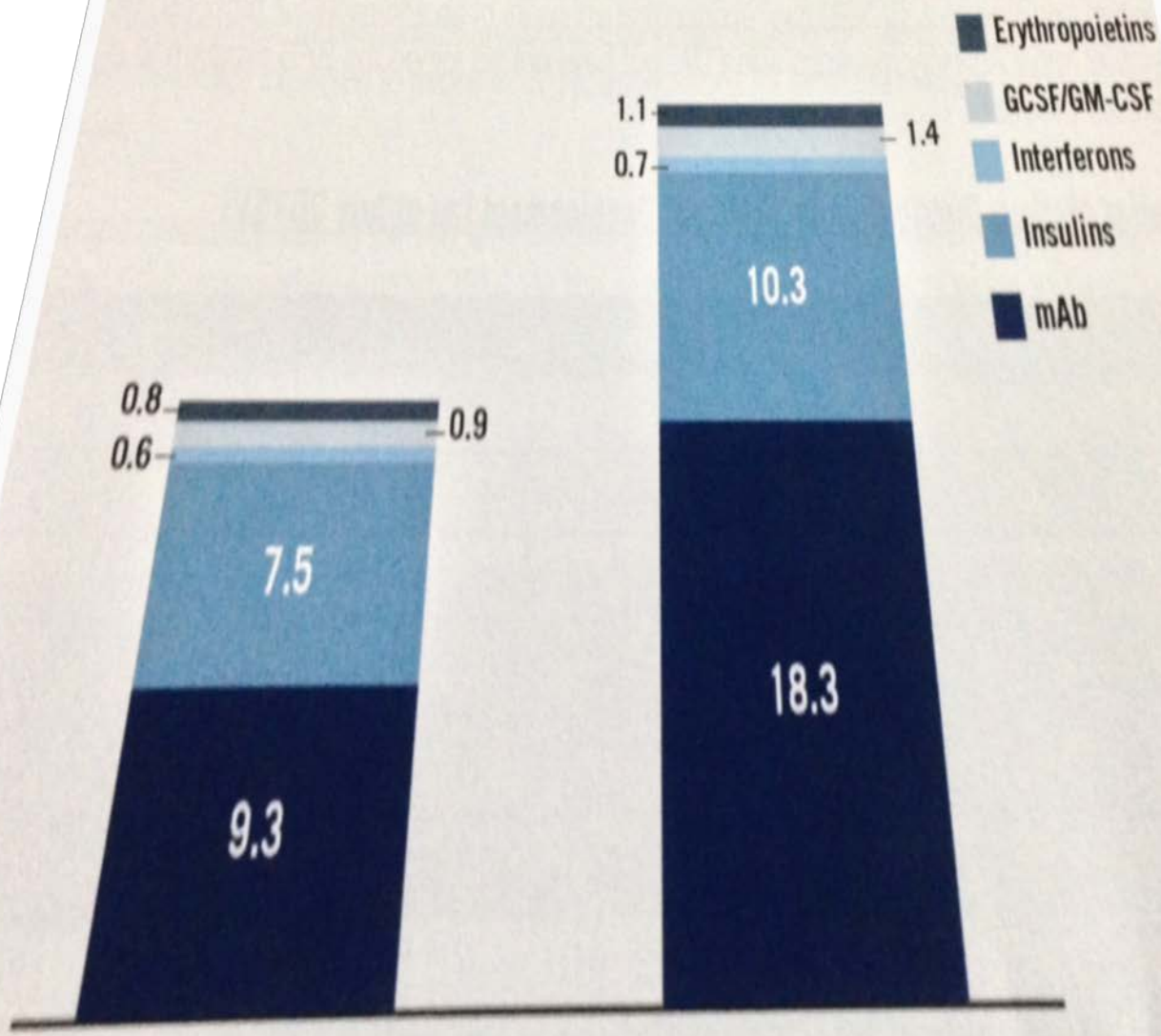
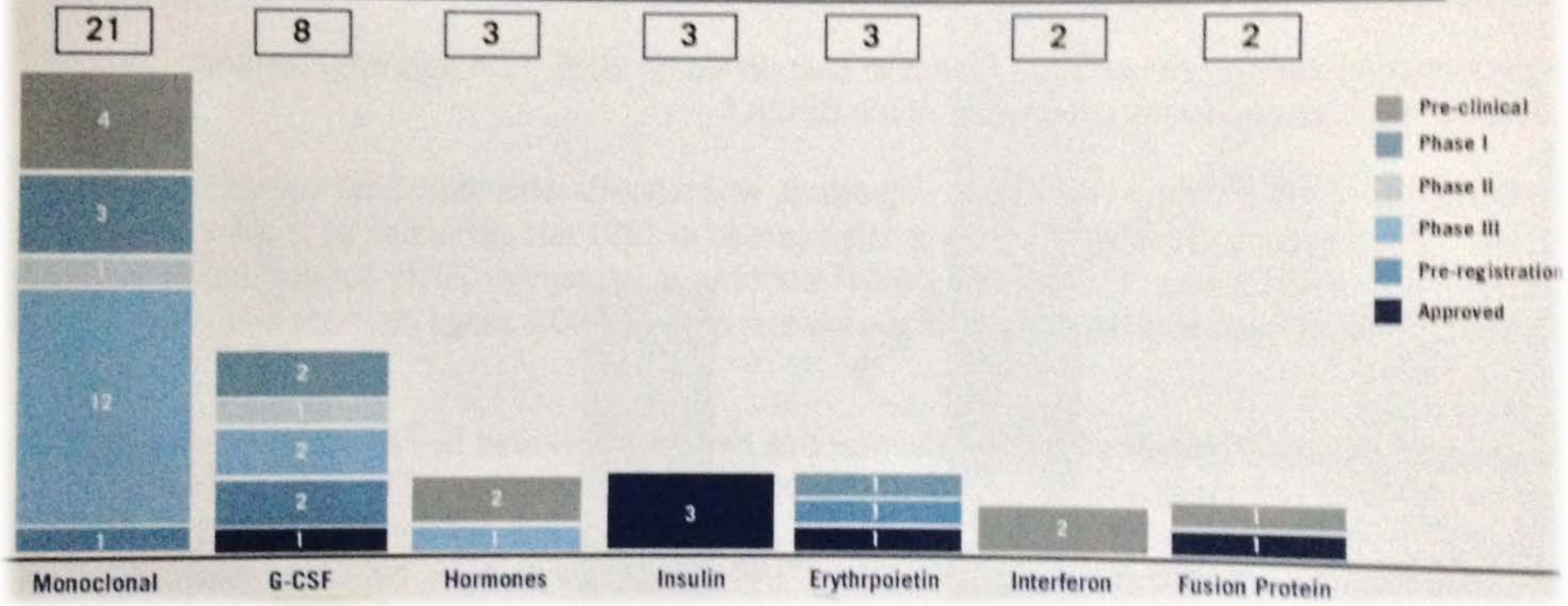


Figure 14.4 the US Biosimilar Market:
Distribution by Product Category



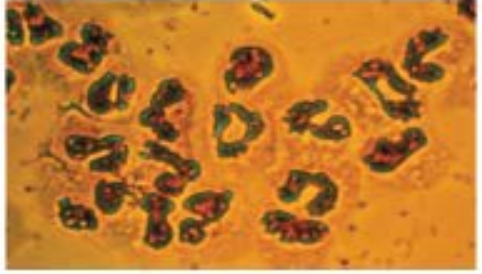
THE NEW COPYCATS

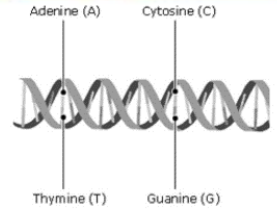
Engineering **BIOSIMILARS,** or near copies, of leading biologic drugs, pushes the limits of bioprocessing know-how

KEY TARGETS Developers are trying to create functional replicas of leading biologic drugs.

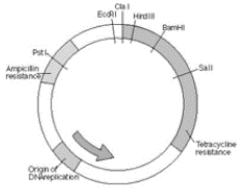
Approved drug	Use	2012 Sales ($ billions)	Originator & major marketers	Patents expire U.S.	Patents expire EU	Biosimilars in development	Major players/partners in biosimilars for regulated markets
Humira (adalimumab)	Inflammatory diseases	9.3	AbbVie	2016	2018	16	Amgen, BioXpress, Boehringer Ingelheim, Fujifilm Kyowa Kirin Biologics, Pfizer
Remicade (infliximab)	Inflammatory diseases	8.2	Johnson & Johnson, Merck & Co.	2018	2015	9	Amgen, BioXpress, Celltrion/Hospira, Pfizer, Samsung Bioepis
Enbrel (etanercept)	Inflammatory diseases	8.0	Amgen, Pfizer	2019	2015	21	BioExpress, Samsung Bioepis, Sandoz
Rituxan (rituximab)	Cancers, arthritis	7.4	Biogen Idec, Genentech, Roche	2018	2013	34	Amgen/Actavis, Biocad, BioXpress, Boehringer Ingelheim, Pfizer, Sandoz, Stada/Gedeon Richter
Herceptin (trastuzumab)	Cancers	6.5	Genentech, Roche	2019	2015	30	Amgen/Actavis, Biocad, Biocon, BioXpress, Celltrion/Hospira, Pfizer, Stada/Gedeon Richter
Avastin (bevacizumab)	Cancers	6.3	Genentech, Roche	2019	2022	16	Amgen/Actavis, Biocad, BioXpress, Boehringer Ingelheim, Fujifilm Kyowa Kirin Biologics

SOURCES: Company data, Biotechnology Information Institute

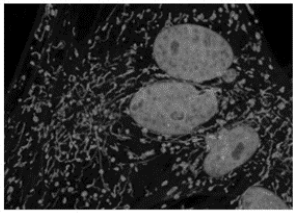





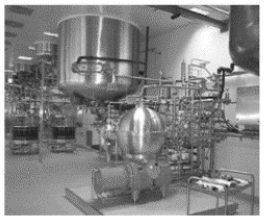
Choice of sequence



Cloning

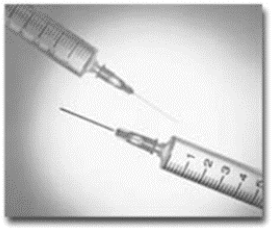


Cell expression



Fermentation

Purification



Formulation

From: The protein science of biosimilars
Nephrol Dial Transplant. 2006;21(suppl_5):v4-v8. doi:10.1093/ndt/gfl474

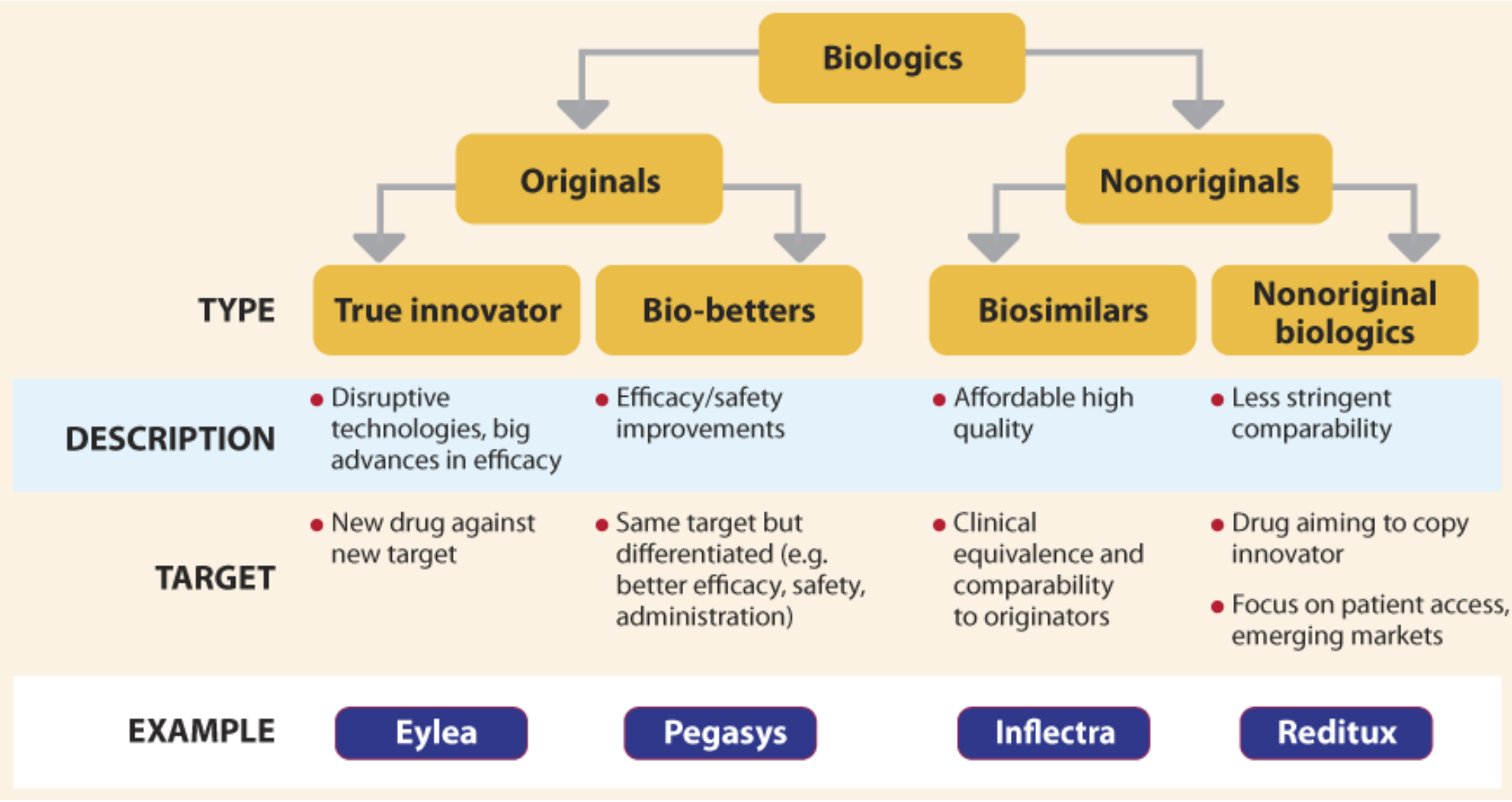
Myths vs. Facts: About Biosimilars

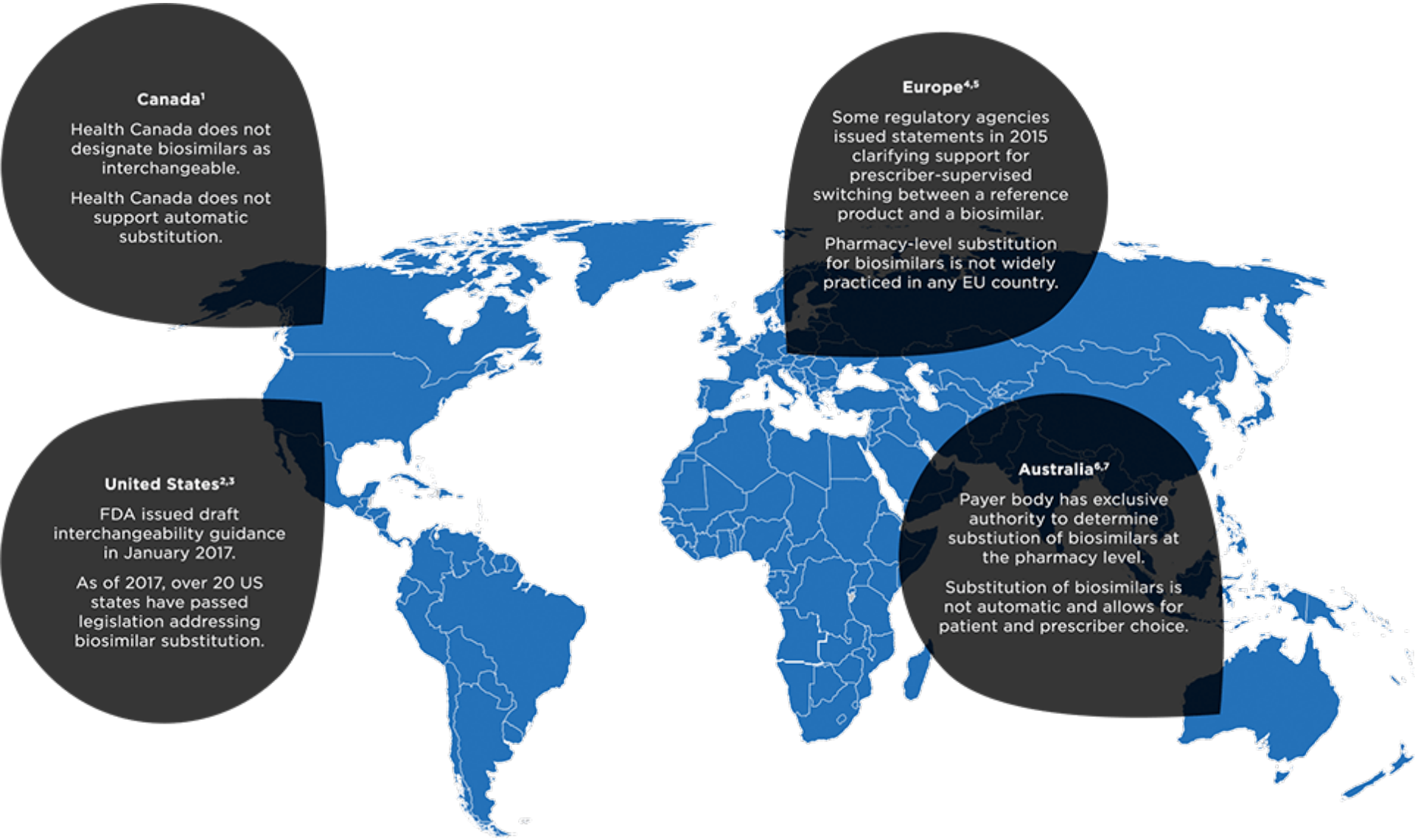
Biosimilars are safe, effective alternative versions of existing brand biologic medicines (known as "reference products") with scientifically comparable quality, safety and effectiveness. Biologic medicines are expensive for patients, taxpayers and insurers. Biosimilars provide important competition, which can help lower costs and increase patient access to lifesaving medications.

What are biosimilars?

A biosimilar is a biologic medicine that is highly similar to a brand biologic medicine. FDA has approved 5 biosimilars[1] to treat Crohn's Disease, cancer, psoriasis and other conditions; 60+ more in development.[2,3]

Myths	Facts
"Biosimilars are less safe for patients than brand biologics."	Biosimilars undergo **rigorous FDA testing, review and safety monitoring.** The biosimilars development process is complex and companies that manufacture biosimilars are committed to providing safe, effective products to patients.
"Biosimilars aren't as effective as brand biologics."	**10+ years** of patient use of biosimilars in the EU has shown no difference in health outcomes between patients who use a biosimilar and those who take the original branded biologic medicine.[4]
"Biosimilars may offer patients *some* savings, but not enough."	Experts estimate that biosimilars will be priced 10 to 35% less than their brand drug prices.[5] Consumers could save as much as **$250 billion** in the next decade.[6]


Biologics
Originals
Nonoriginals
TYPE
True innovator
Bio-betters
Biosimilars
Nonoriginal biologics
DESCRIPTION
• Disruptive technologies, big advances in efficacy
• Efficacy/safety improvements
• Affordable high quality
• Less stringent comparability
TARGET
• New drug against new target
• Same target but differentiated (e.g. better efficacy, safety, administration)
• Clinical equivalence and comparability to originators
• Drug aiming to copy innovator
• Focus on patient access, emerging markets
EXAMPLE
Eylea
Pegasys
Inflectra
Reditux


Canada[1]
Health Canada does not designate biosimilars as interchangeable.
Health Canada does not support automatic substitution.
Europe[4,5]
Some regulatory agencies issued statements in 2015 clarifying support for prescriber-supervised switching between a reference product and a biosimilar.
Pharmacy-level substitution for biosimilars is not widely practiced in any EU country.
United States[2,3]
FDA issued draft interchangeability guidance in January 2017.
As of 2017, over 20 US states have passed legislation addressing biosimilar substitution.
Australia[6,7]
Payer body has exclusive authority to determine substiution of biosimilars at the pharmacy level.
Substitution of biosimilars is not automatic and allows for patient and prescriber choice.

With the passage of the Biologics Price Competition and Innovation Act of 2009, the US Food and Drug Administration established an abbreviated pathway for developing and licensing biosimilar and interchangeable biological products. The regulatory framework and the technical requirements of the US biosimilars program involve a stepwise approach that relies heavily on analytical methods to demonstrate through a "totality of the evidence" that a proposed product is biosimilar to its reference product. By integrating analytical, pharmacological, and clinical data, each of which has limitations, a high level of confidence can be reached regarding clinical performance. Although questions and concerns about the biosimilars pathway remain and may slow uptake, a robust scientific program has been put in place. With three biosimilars already licensed and numerous development programs under way, clinicians can expect to see many new biosimilars come onto the US market in the coming decade. [Note added in proof: Since the writing of this article, a fourth biosimilar has been approved.]

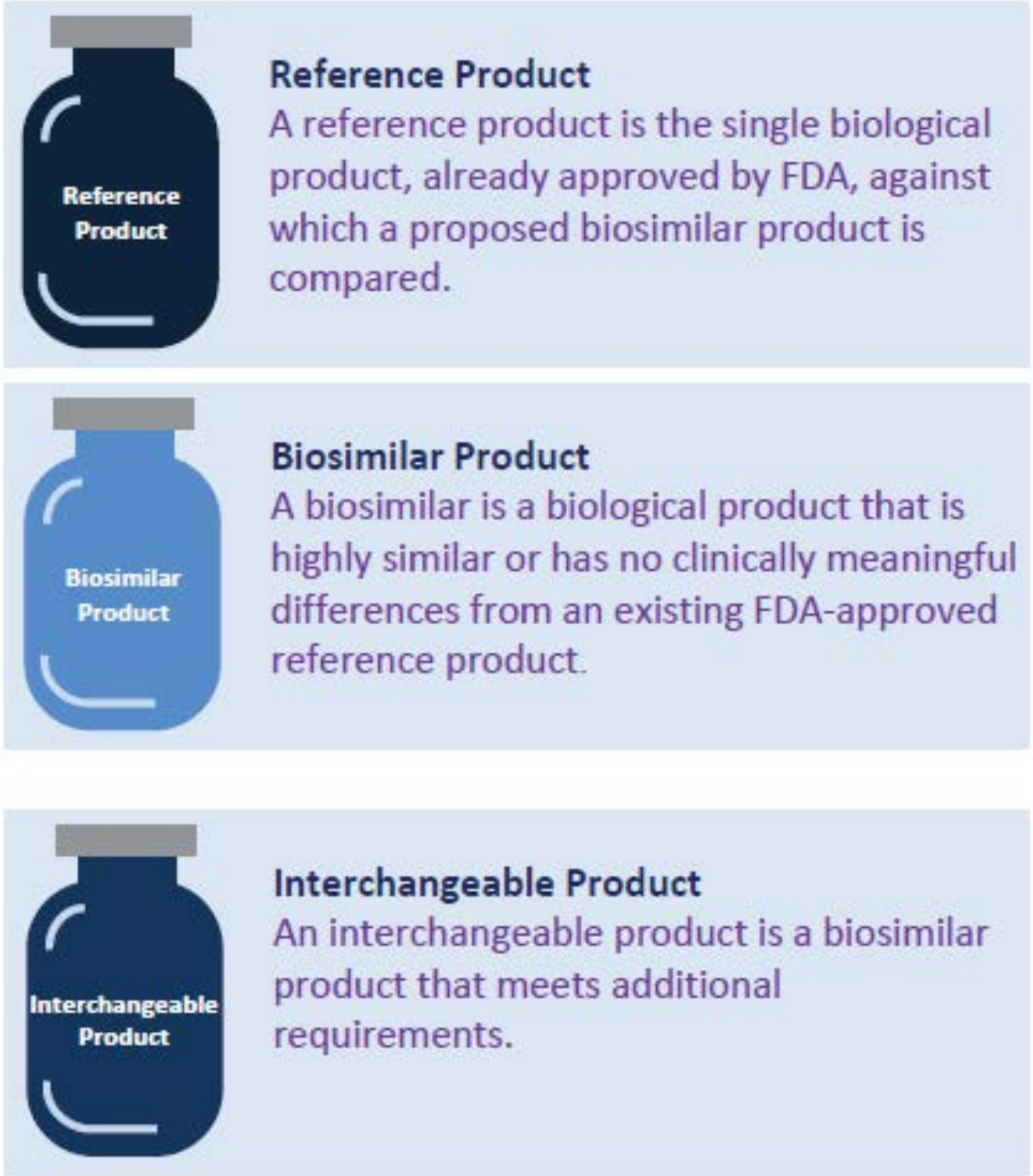


Figure 1.12 FDA Terminology regarding biosimilars.

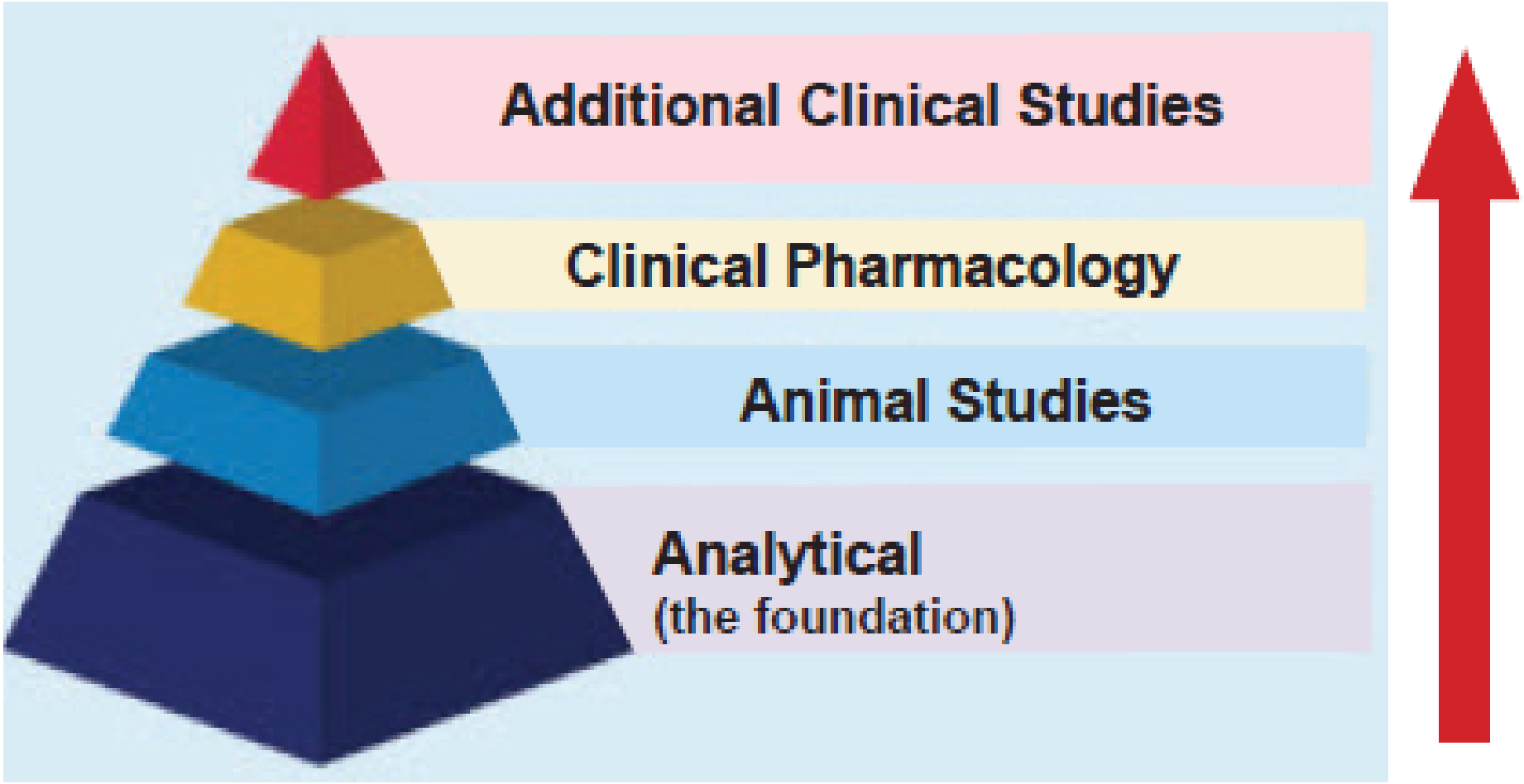


Figure 1.13 The FDA's review for licensure of a biosimilar product.

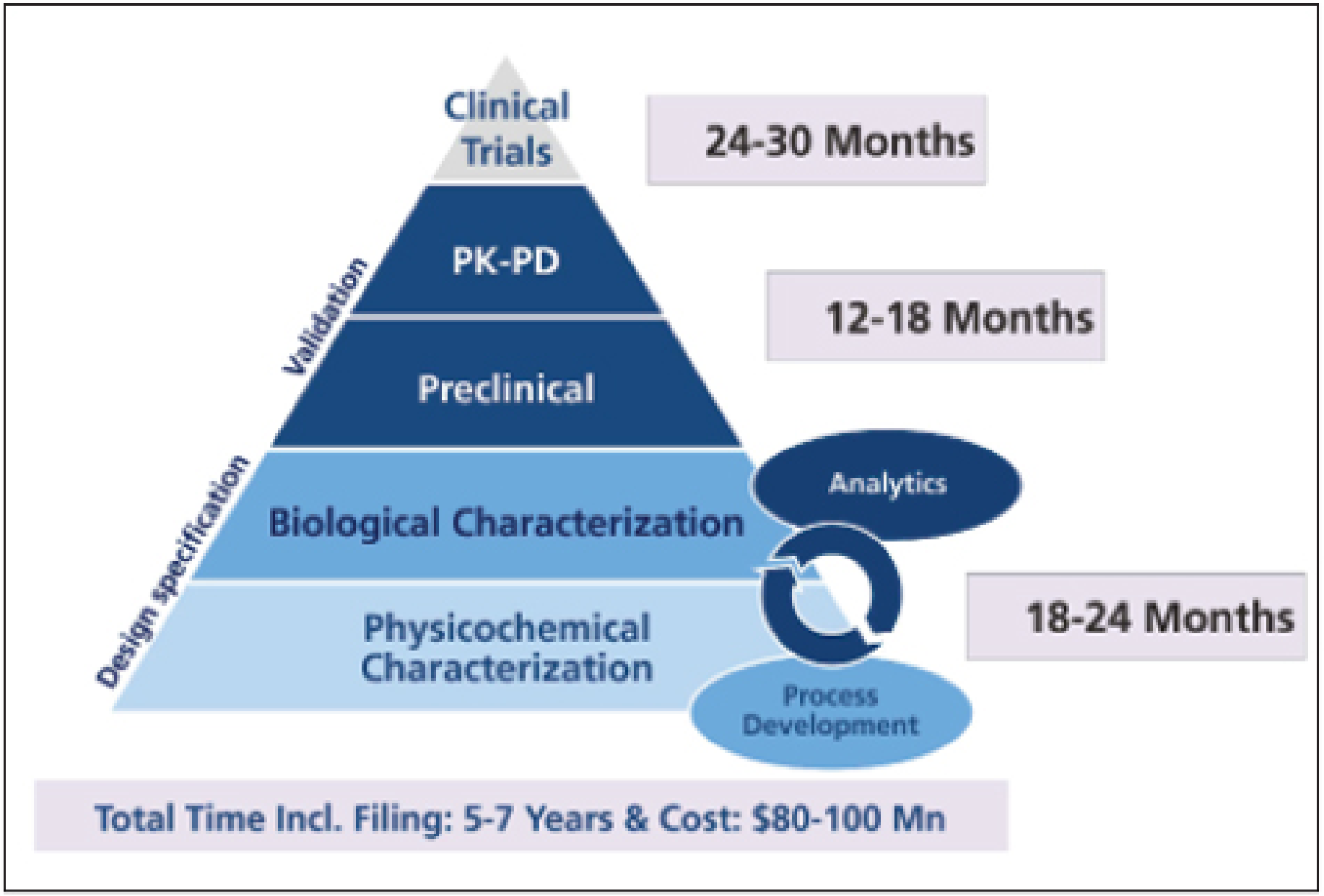
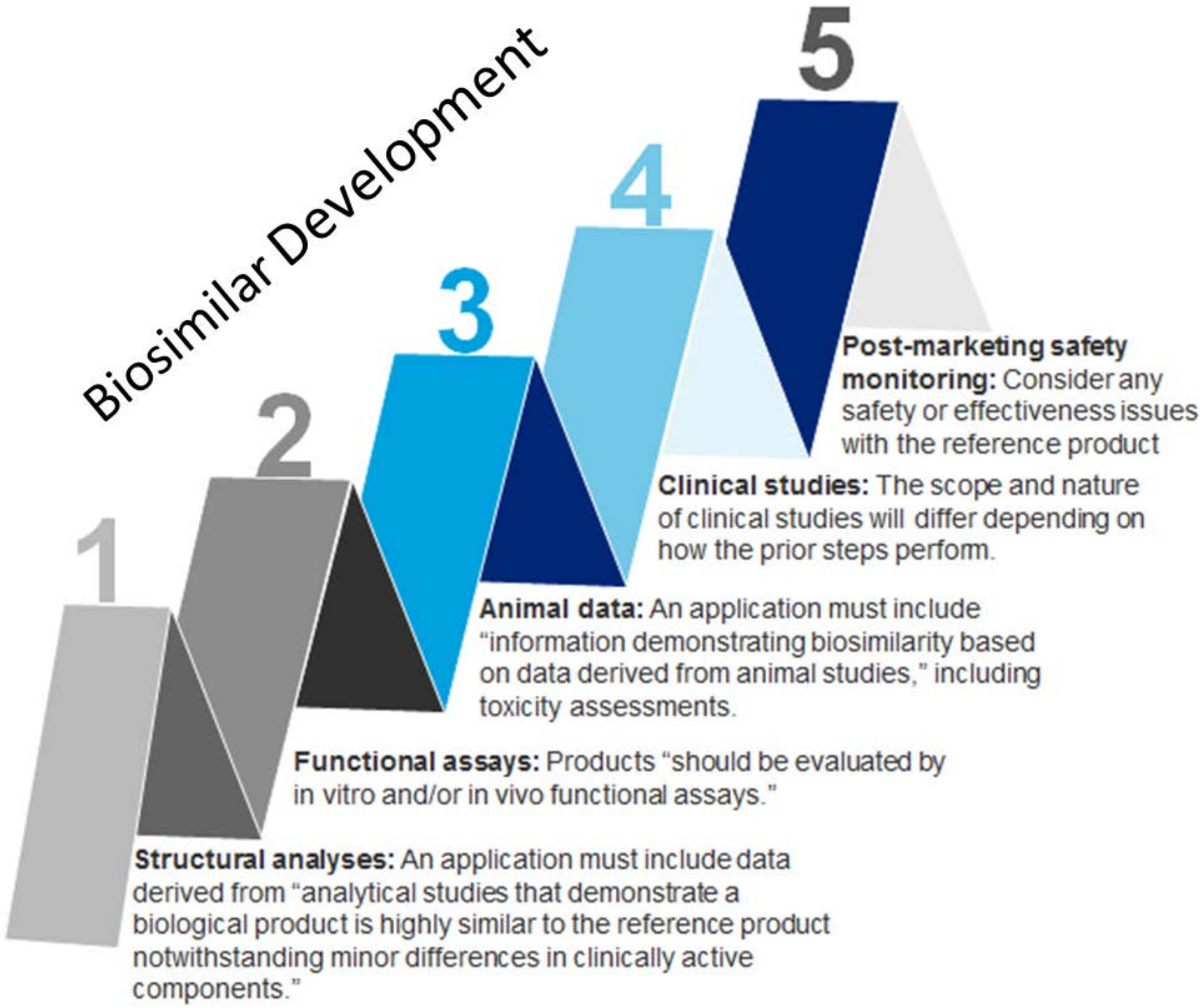
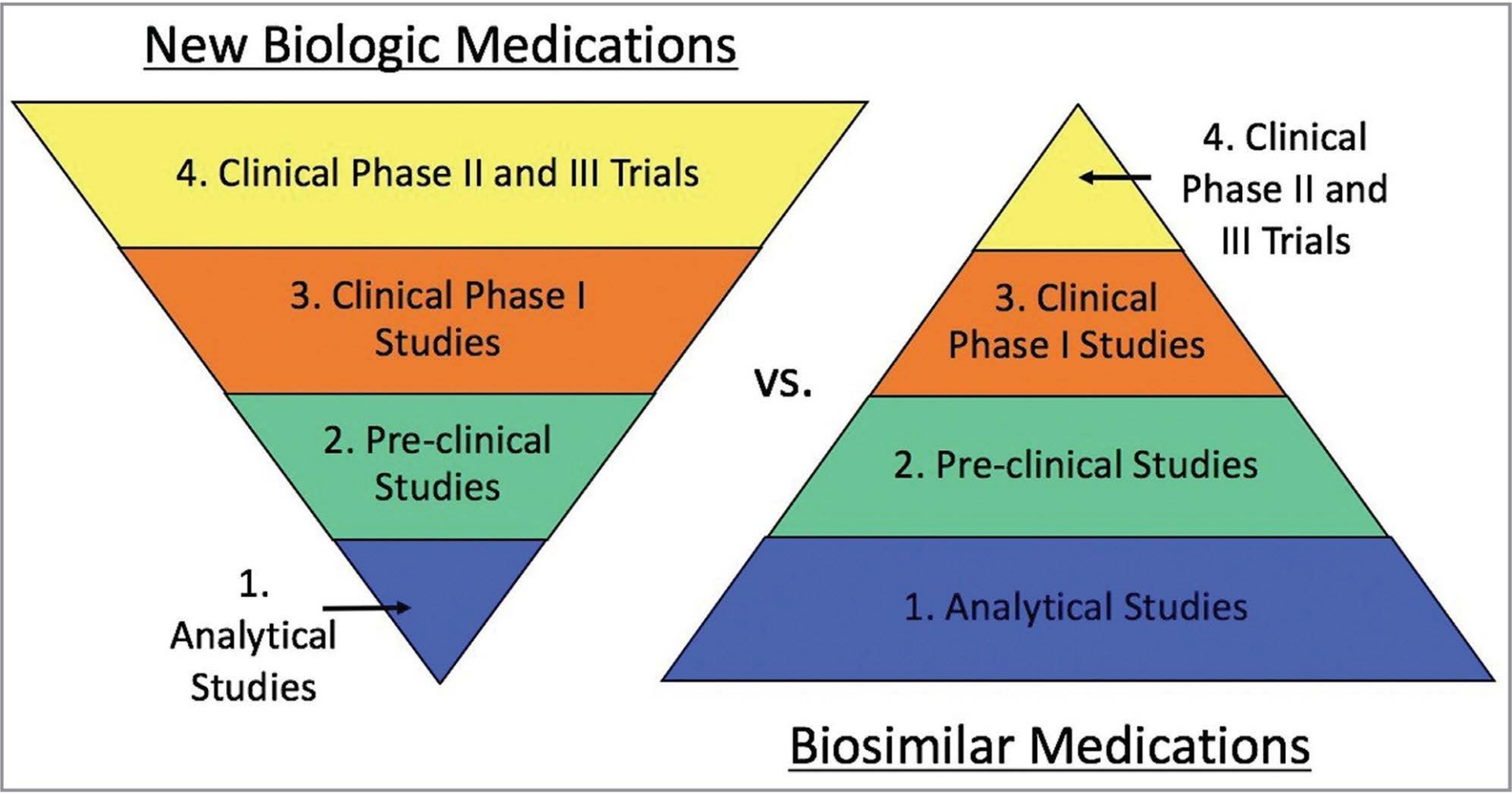


Figure 2: Biosimilars: An Abbreviated Pathway (Reality or Mirage)


Biosimilar Development
1
2
3
4
5
Structural analyses: An application must include data derived from "analytical studies that demonstrate a biological product is highly similar to the reference product notwithstanding minor differences in clinically active components."
Functional assays: Products "should be evaluated by in vitro and/or in vivo functional assays."
Animal data: An application must include "information demonstrating biosimilarity based on data derived from animal studies," including toxicity assessments.
Clinical studies: The scope and nature of clinical studies will differ depending on how the prior steps perform.
Post-marketing safety monitoring: Consider any safety or effectiveness issues with the reference product


New Biologic Medications
4. Clinical Phase II and III Trials
3. Clinical Phase I Studies
2. Pre-clinical Studies
1. Analytical Studies
vs.
4. Clinical Phase II and III Trials
3. Clinical Phase I Studies
2. Pre-clinical Studies
1. Analytical Studies
Biosimilar Medications

BIOEQUIVALENCE

The primary difference between an ANDA compared to a New Drug Application is the requirement for bioequivalence data (**Figure 2**).[1]

Figure 2

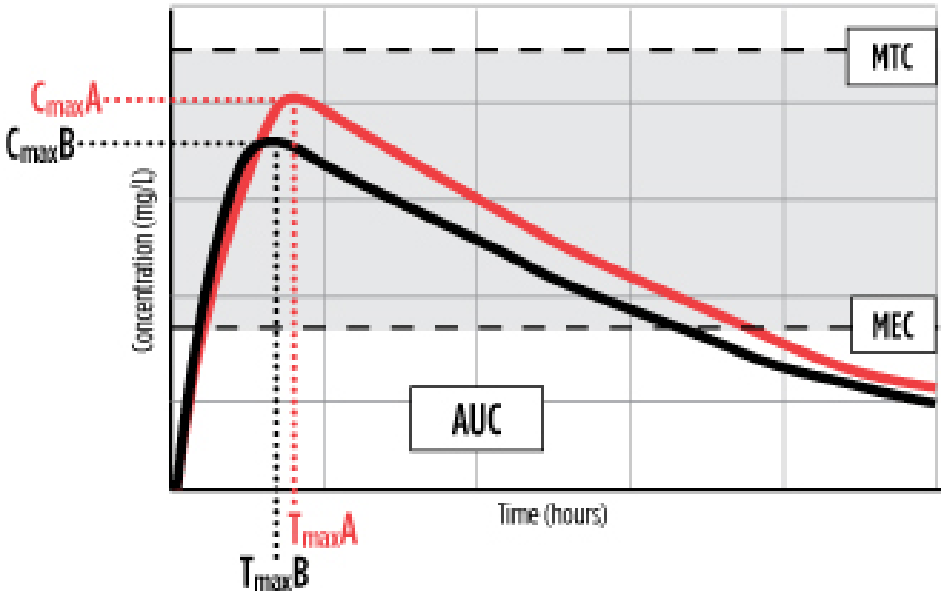
COMPARISON OF FDA APPROVAL REQUIREMENTS

Brand Requirements	Generic Requirements
• Chemistry	• Chemistry
• Manufacturing/Production standards	• Manufacturing/Production standards
• Controls	• Controls
• Labeling	• Labeling
• Testing (eg, potency, shelf-life)	• Testing (eg, potency, shelf-life)
• Animal Studies	
• Clinical Studies	**• Bioequivalence**
• Bioavailability	

Source: Buehler 2007.[1]

- For bioequivalence, similarities of a brand-name drug and a generic drug should fall within a 90% CI (Confidence Interval), where AUC (amount absorbed) and Cmax (peak concentration) are at most 20% more or less than levels established by the brand-name drug[1]
  - Analysis is based on the 2 one-sided tests approach, which tests and rejects the null hypothesis (treatments are not equivalent) to prove bioequivalence[3]

- **1.** Buehler GJ, Conner D. The Food and Drug Administration process for approving generic drugs. [Online training seminar]. Office of Generic Drugs. US Food and Drug Administration. Published June 2007. Updated June 18, 2009. http://www.fda.gov/Training/ForHealthProfessionals/ucm090320.htm. Accessed December 30, 2010.
- **3.** Patel J, Aneja K, Tiwari R. Bioavailability and bioequivalence trials and its necessity. *Intern J Pharmacy Pharm Sci.* 2010;2(3):1-8.



Bioequivalence at a Glance

Originator — Generic

Tmax: time required to achieve the maximum concentration.

MTC: minimum toxic concentration.

MEC: minimum effective concentration.

Shaded area: the therapeutic window for which efficacy and safety have been established.

BOX 1. Glossary of terms

Bioequivalence (BE) is considered to be demonstrated if the 90% confidence intervals of the ratios for log AUC_{0-t} and C_{max} between the two preparations lie in the range 80.00–125.00%, correlating to a 90% BE confidence interval.[40]

Dynamic light scattering is a technique to determine the size distribution profile of small particles in suspension. A laser beam illuminates the suspension, and the fluctuations of the scattered light are detected by a fast photon detector.

Nanomedicine is a medicinal product developed and manufactured using nanomaterials and nanotechnology and often comprising multiple structures, biological or nonbiological.

Nanosimilar is a follow-on product of a reference nanomedicine.[4]

NBCD. A medicinal product, not being a biological medicine, where the active substance is not a homomolecular structure, but consists of different (closely) related and often nanoparticulate structures that cannot be isolated and fully quantitated, characterized, and/or described by physicochemical analytical means. It is also unknown which structural elements might affect the therapeutic performance. The composition, quality, and *in vivo* performance of NBCDs are highly dependent on the manufacturing processes of both the active ingredient and the formulation. Examples of NBCDs include liposomes, iron–carbohydrate (iron–sugar) drugs, and glatiramoids.[40]

Interchangeability at the ***individual level*** means that, in an individual patient, two medicinal products that are believed to be therapeutically equivalent can be alternated or switched with the authorization of the initial prescriber. Interchangeability at the individual level is a condition for substitution.[40,41]

Interchangeability at the ***population level*** means that two medicinal products that are believed to be therapeutically equivalent can be used for treatment for the same condition in the same population.[40]

Pharmaceutical equivalence implies the same amount of the same active substance(s), in the same dosage form, for the same route of administration and meeting the same or comparable standards.

Substitutability means a dispensing policy to allow replacement at the individual level of a medicinal product for a similar/bioequivalent medicinal product without the prior authorization of the initial prescriber.[40,41]

Switchability means that the product can be changed (e.g., from reference product to biosimilar or vice versa) in a patient during the course of treatment.[40]

Therapeutic equivalence of two different products enables the products to be interchanged. Two medicinal products with systemic effects are therapeutically equivalent if they are pharmaceutically equivalent and if their bioavailabilities after administration at the same molar dose are similar to such a degree that their effects, with respect to both efficacy and safety, will be essentially the same (bioequivalent).[40]

Zeta potential is the electric potential of the surface of a (solid) particle immersed in a liquid relative to a point in the bulk fluid away from the interface.

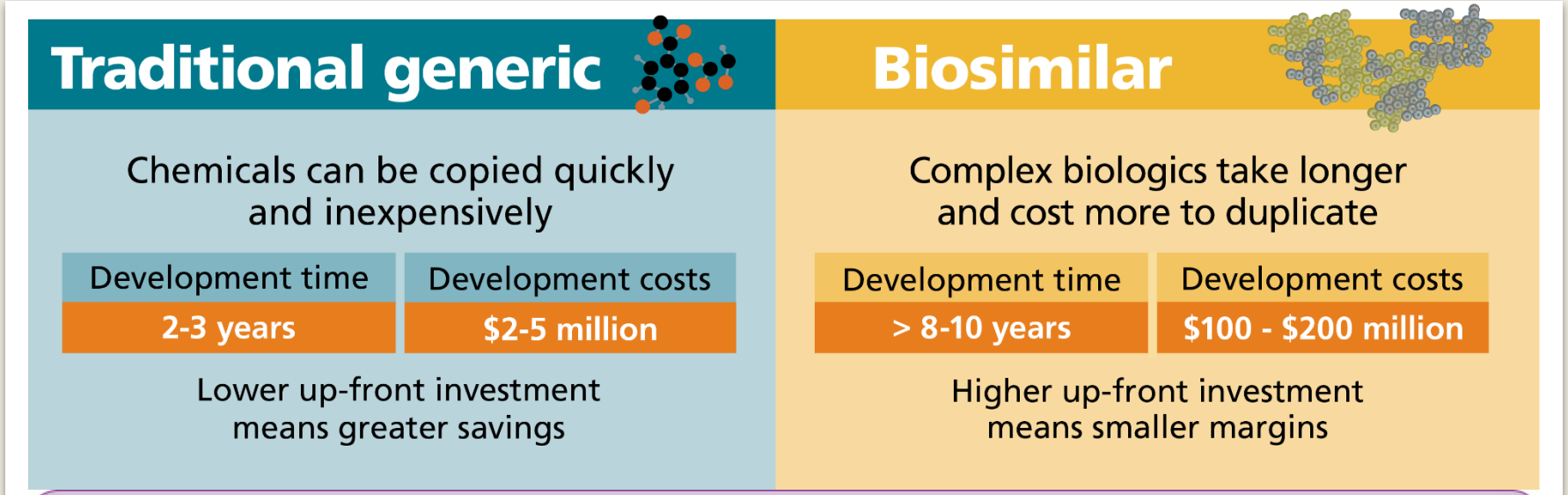
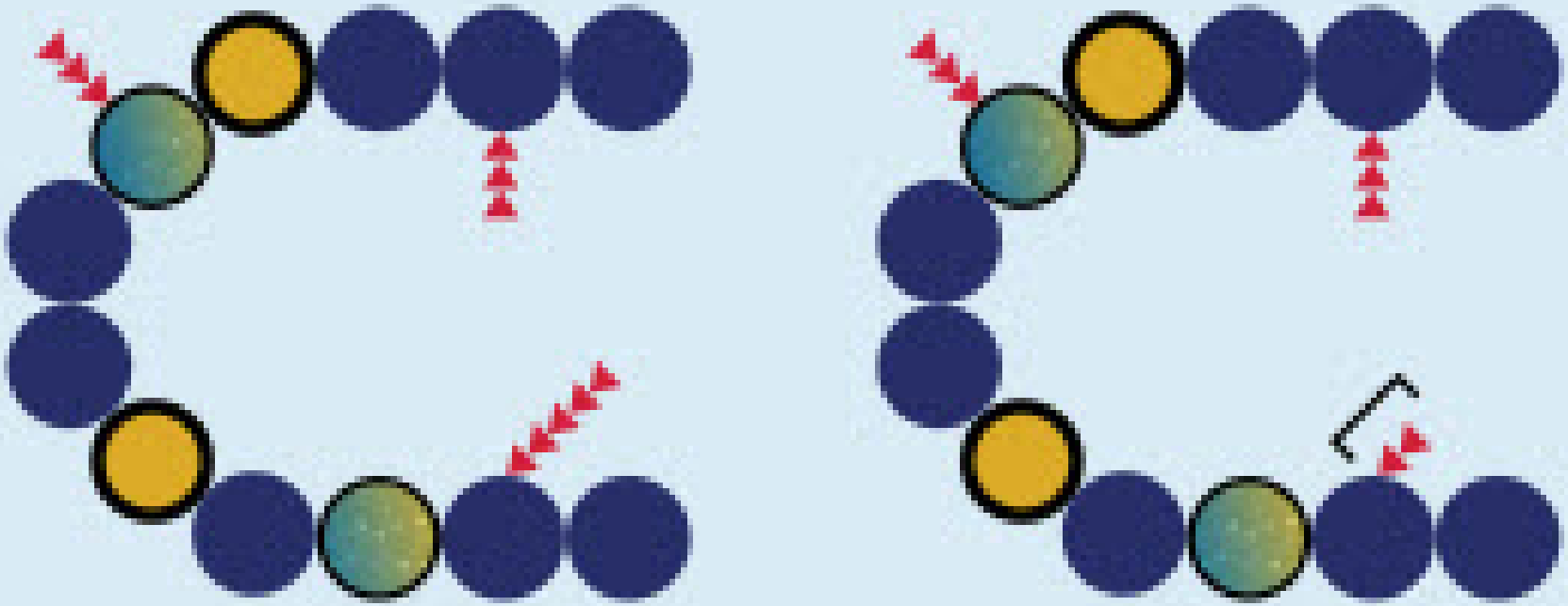


Table 1. Comparison of Generic Drugs vs. Biosimilars

	Generics	Biosimilars
Molecular structure	Simple structure; low molecular weight	Complex structure; large molecular weight proteins
	Can create identical copies	Minor variations in molecular composition may occur; this can also occur from lot to lot with reference biologics
FDA approval process	No clinical efficacy trials required for approval; focus on pharmacokinetics	Clinical trials necessary
	When approved, all indications apply	Manufacturers must apply for extrapolation across indications
	Substitution directed by Orange Book	Substitution directed by Purple Book
Health-care costs	Costs to bring to market relatively low	Costs to bring to market very high

Note. FDA = US Food and Drug Administration. Adapted from Rumore & Vogenberg (2016).



Brackets are used to show sites with minor variations.

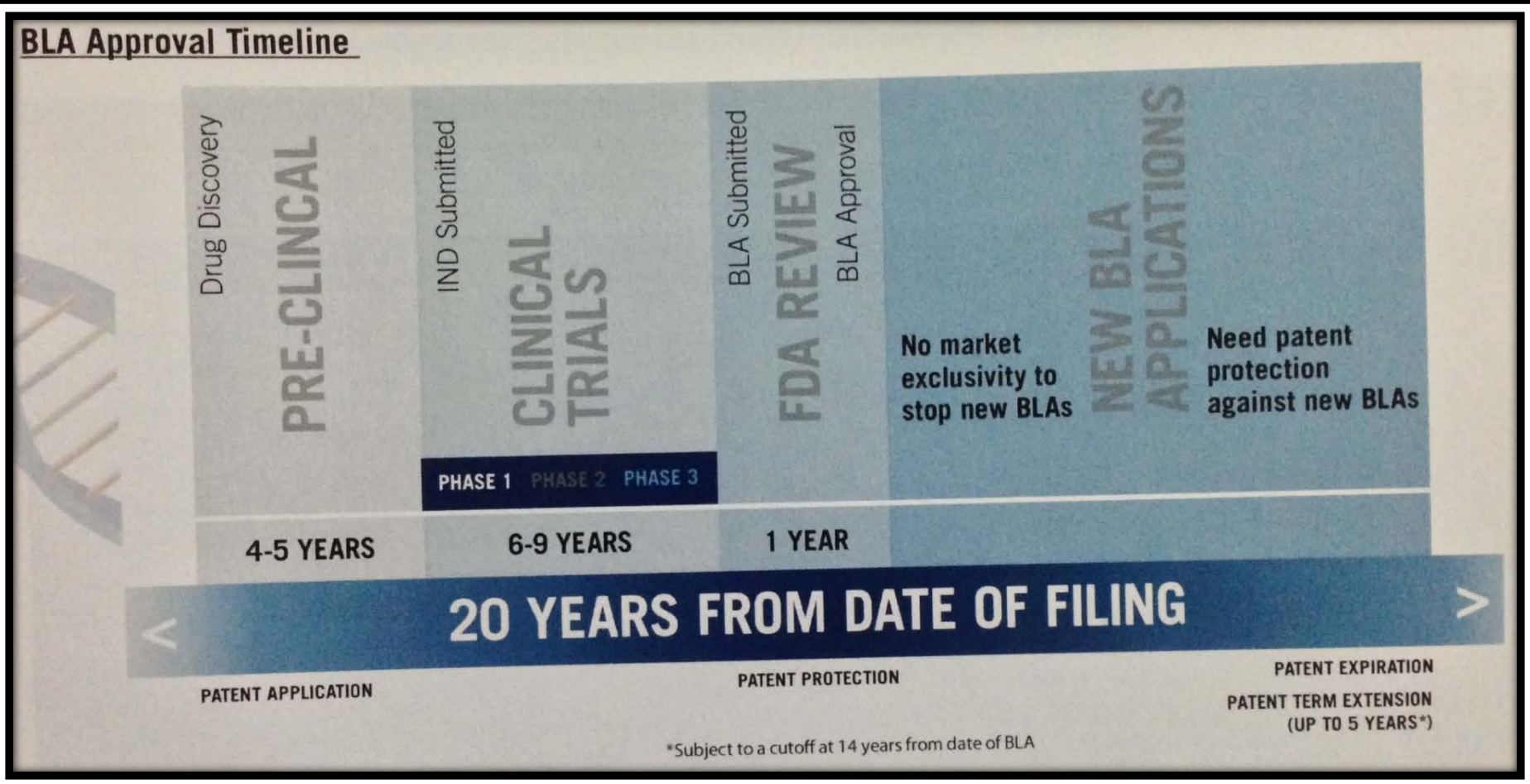
Reproduced with permission from the European Medicines Agency

Minor differences between the references product and the proposed biosimilar product in clinically inactive components are acceptable.

The Approval Process in a Nutshell

- ✓ The approval process for biosimilars allows the submission of a biological license application for a biosimilar or interchangeable biological.
- ✓ The process requires a biosimilar applicant to demonstrate that there are no clinically meaningful differences in safety, purity, or potency between a biosimilar product and the branded product. A demonstration of biosimilarity requires analytical data, animal testing, and clinical studies, unless a requirement is determined to be unnecessary.
- ✓ The process allows approval of a biosimilar product as interchangeable either at the time of initial approval or after a supplemental approval. An interchangeable product is a biosimilar product that can be substituted for the branded product without the intervention of the health care provider who prescribed the branded product. A demonstration of interchangeability requires evidence that the biosimilar product will produce the same clinical result as the branded product in any given patient and that it presents no additional risk if a patient is switched between products.

BLA Approval Timeline



Comparison of Approval Pathways and Timelines

The table below sets forth the differences between the 262(k), 262(a), and ANDA/paper NDA pathways.

Comparison Between the BLA 262(a) Pathway and Biosimilar 262(k) Pathway

	262(a) Application	262(k) Application
Goal	The goal of "stand-alone" development is to demonstrate that the proposed product is safe and efficacious.	The goal is to demonstrate biosimilarity between the proposed product and the reference product.
Clinical studies	Clinical studies are required. Drug development starts with preclinical research, moves to Phase 1, 2 and culminates in Phase 3 "pivotal" trials to show safety and efficacy.	The goal is not independently to establish safety and effectiveness of the proposed product. Any comparative clinical study for a biosimilar development program should be designed to investigate whether there are clinically meaningful differences in terms of safety, purity and potency between the proposed product and the reference product. The nature and scope of the comparative clinical studies will depend on the extent of residual uncertainty about the biosimilarity of the proposed product and reference product after conducting structural and functional characterization and, if relevant, animal studies.
Timing of application	A 262(a) application can be filed and approved any time.	A 262(k) application cannot be filed for four years after the reference product is approved, and the biosimilar product cannot be approved for 12 years after that approval.
Advantages	Predictability.	Potential indication extrapolation and interchangeability designation.
Comparison to reference product	No need to be biosimilar to a reference product.	Must be biosimilar to a reference product.
Track record	FDA has approved follow-on biologics under the 262(a) pathway.	So far FDA has approved one biosimilar under the 262(k) pathway: Sandoz's biosimilar product Zarxio®, referencing Amgen's Neupogen® product (approved March 6, 2015).

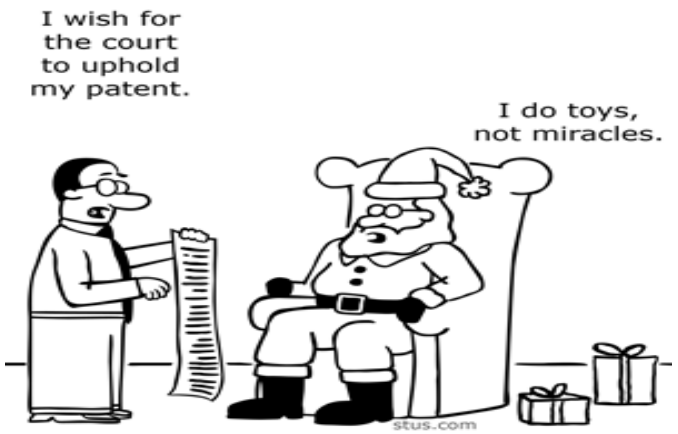
Comparison Between the 262(a) Pathway and the ANDA Pathway

Provision	Hatch-Waxman Route (505(j) Application)	Biosimilar Route (262(k) Application)
Drug	Generic drug must be bioequivalent to an approved brand drug.	Biosimilar must be highly similar to the reference product notwithstanding differences in clinically inactive components and there can be no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.
Regulatory law	Hatch-Waxman Act of 1984 of the Food, Drug, and Cosmetic Act.	Biologics Price Competition and Innovation Act of the Public Health Service Act of 2009.
Application	Abbreviated New Drug Application - 505(j) application.	262(k) application.
Timing of first application	ANDA can be filed four years after FDA approval of reference product if paragraph IV certification; otherwise, five years.	Biosimilar application can be filed four years after FDA approval of reference product.
Reference product exclusivity	• 5-year marketing exclusivity for new chemical entity • 6 months for pediatric exclusivity • 7 years for orphan drug exclusivity	• 12-year marketing exclusivity for new biologic • 6 months for pediatric exclusivity • 7 years for orphan drug exclusivity
Generic drug exclusivity	180 days if first to file and to certify under Paragraph IV challenging an Orange Book-listed patent.	Only if interchangeable – time is variable but intent is to give one year.
Orange Book	Orange Book listing of patents; certification by generic applicant.	No Orange Book; private exchange of patent information.[26]
Patent certifications	An ANDA applicant must make a certification addressing each patent listed in the Orange Book that claims the reference drug. The ANDA applicant must certify that (I) no such patent information has been submitted to FDA; (II) the patent has expired; (III) the patent is set to expire on a certain date; or (IV) the patent is invalid or will not be infringed by the manufacture, use, or sale of the new generic drug for which the ANDA is submitted. These are commonly referred to as paragraph I, II, III, and IV certifications.	A biosimilar applicant need not certify against any patents but may exchange with the BLA holder certain information on patents identified by the parties, and negotiate in an attempt to agree on a list of patents to be included in the first phase of litigation. This complicated and controversial process is discussed in more detail in the following pages.
Stay upon filing of suit	Automatic 30-month stay.	No automatic stay.

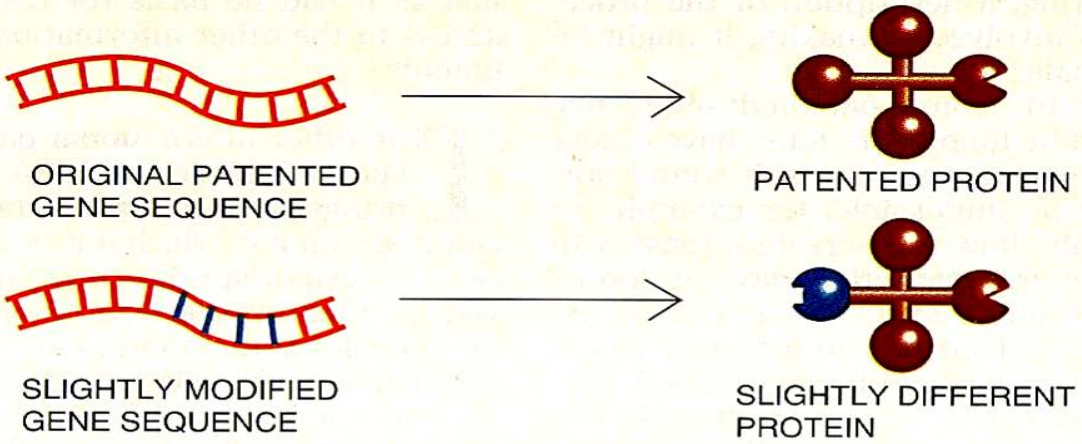
Provision	Hatch-Waxman Route (505(j) Application)	Biosimilar Route (262(k) Application)
Exchange of contentions	NDA holders are required to list all patents that claim the drug or method of using the drug in the Orange Book, and a generic drug applicant seeking to enter the market before expiration are required to notify the NDA holder and provide a detailed analysis as to why it believes each challenged patent is invalid or will not be infringed. The NDA holder is not required to supply a reciprocal factual and legal basis, or otherwise respond to these assertions.	After a biosimilar applicant provides a factual and legal basis for its opinion that BLA-listed patent(s) are invalid, unenforceable or not infringed, the BLA holder itself must provide a factual and legal basis regarding its opinion that patents are infringed, as well as a response to the biosimilar applicant's assertions regarding invalidity and unenforceability.
Notice to launch	No.	180-day notice of intent to market biosimilar.
Option to opt out of statutory litigation scheme	No.	Yes, per the Federal Circuit's opinion in *Amgen v. Sandoz*, discussed in the following pages (whether this notice is mandatory is the subject of ongoing litigation, as discussed in the following pages).

Below is a chart of other targets that may attract biosimilar applications in the U.S. in the near term.

Name	Substance	Company	U.S. Patent Expiration	Global Sales	Developing Biosimilars for U.S.	Status
Humira®	adalimumab	AbbVie	2016	$12.8B	Boehringer Ingelheim	Phase III
					Amgen	Phase III
					Sandoz/Novartis	Phase III
					Coherus Biosciences	Phase I
					Pfizer	Phase I
Remicade®	infliximab	Johnson & Johnson	2018	$9.9B	Hospira/Celltrion	Pre-registration
					Pfizer	Phase III
Rituxan®	rituxamab	Biogen Idec Inc.	2018	$8.7B	Pfizer	Phase III
					Boehringer Ingelheim	Phase III
					Amgen/Actavis	Phase III
					Celltrion	Phase III
					iBio Inc.	Preclinical
Lantus®	insulin glargine	Sanofi SA	Expired	$8.3B	Samsung Bioepsis/ Merck	Phase III
					Eli Lilly	Pre-registration
Neulasta®	pegfilgrastim	Amgen, Inc.	2015	$4.6B	Coherus Biosciences	Phase I
					Pfenex/Agila Biotech	Pre-Clinical
					Sandoz	Pre-registration



What Constitutes Infringement of a Protein Patent?

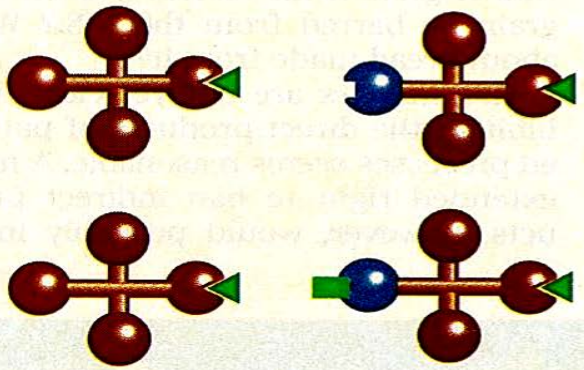


Decisions about whether the modified protein infringes the original patent may depend on its properties.

NO INFRINGEMENTS

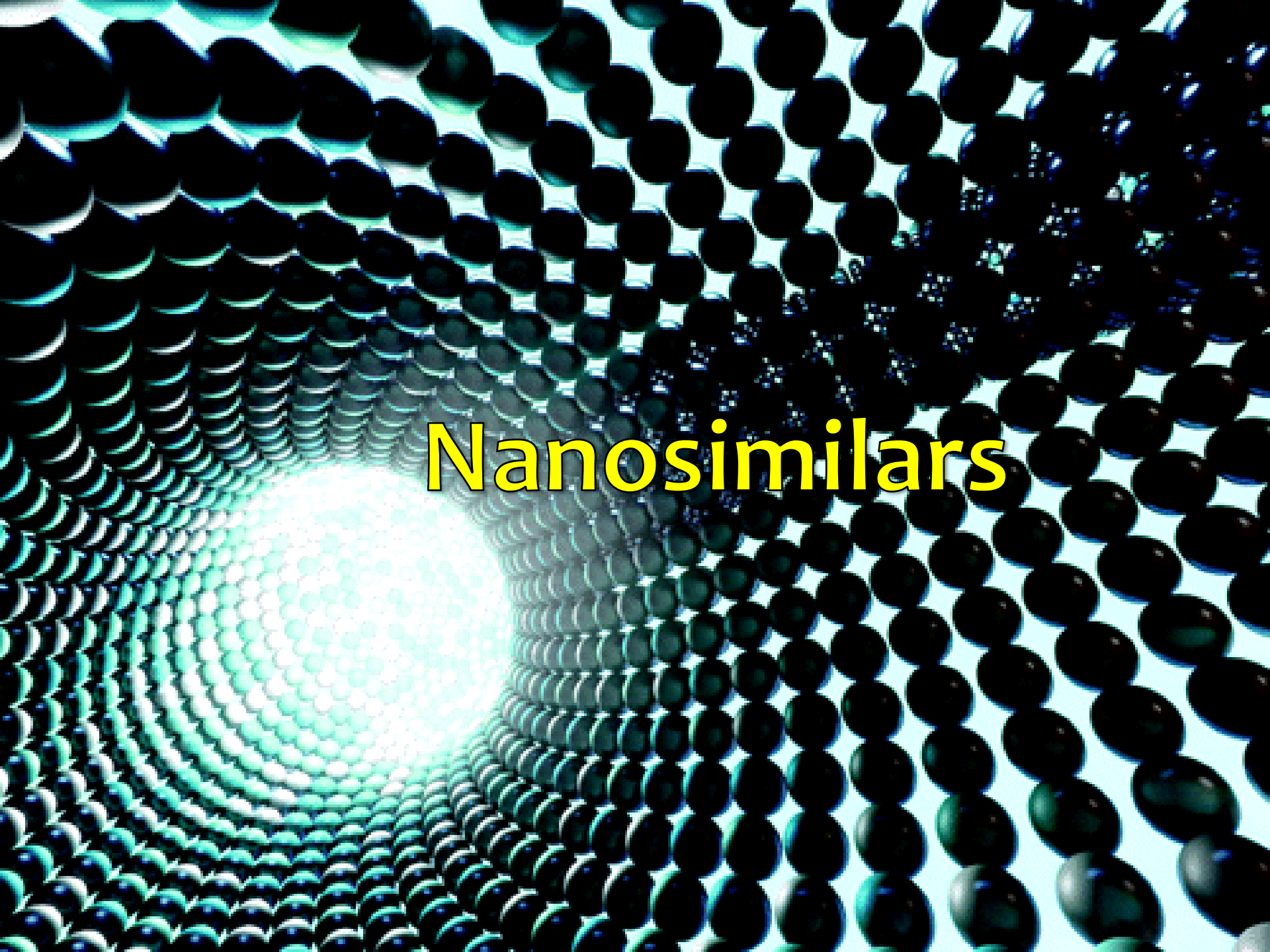
If the proteins have different reactive properties, the modified form may be uniquely patentable itself.

INFRINGEMENT



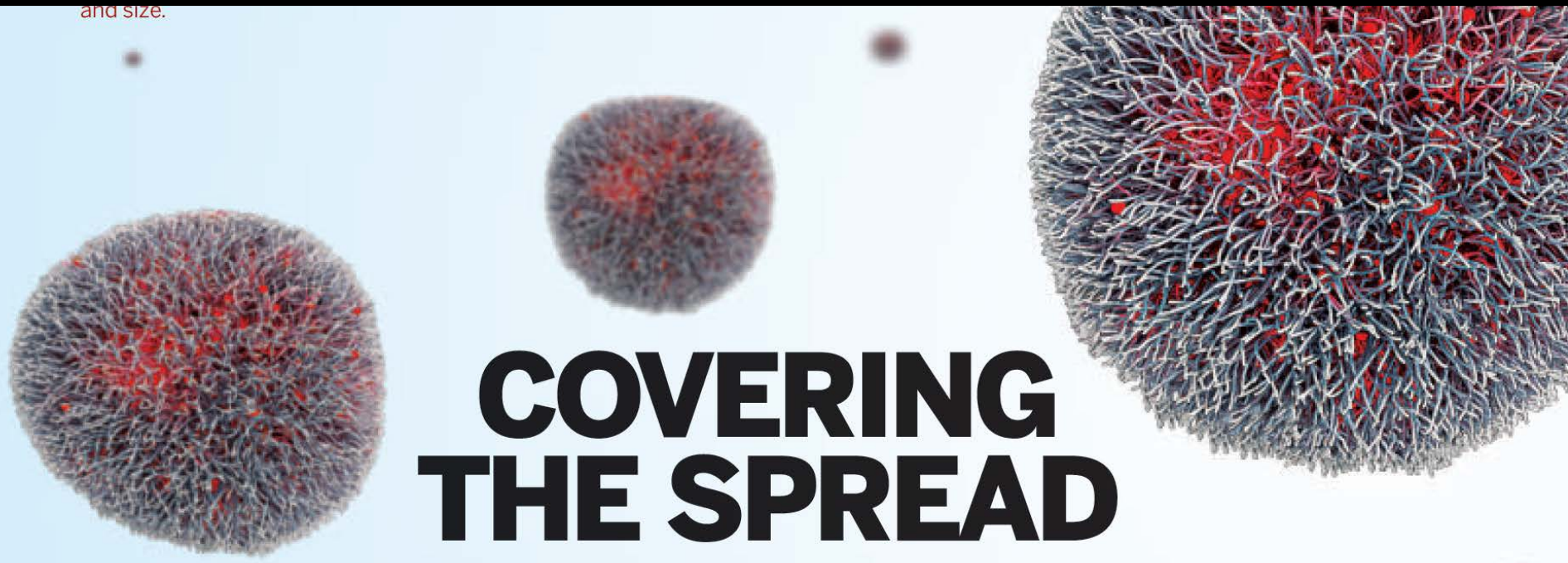
If both proteins have identical reactive properties, the modified version may be an infringement.

If the modified protein has both unique and previously patented features, its maker may not need to pay a licensing fee for some unique applications.


Nanosimilars

Generic Nanomedicines
Nanosimilars/Nanobiosimilars
NBCDs follow-ons

and size.



COVERING THE SPREAD

Variability within—and across—**NANOMEDICINES** is complicating their generics pipeline

MATT DAVENPORT, C&EN WASHINGTON

& MORE ONLINE

For additional images and a more comprehensive list of nanomedicines, go to http://cenm.ag/ndrug.

Nanosimilars - Generic Nanomedicines

- Medicinal products (therapeutics) can be divided into three classes:

- small-molecule drugs (NCEs)
- biologic drugs (NBCs)
- non-biological complex drugs (NBCDs)

- NBCDs more closely resemble biologic drugs than small-molecule drugs.

- Many nanomedicines are NBCDs.

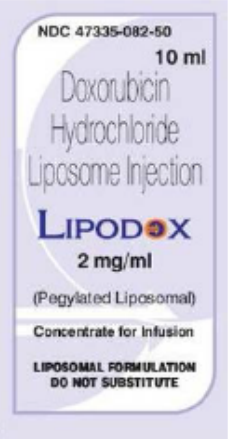
- NBCDs (e.g., liposomal drugs, glatiramoids, and iron-sugar complexes) lack a homo-molecular structure but consist of different yet closely related chemical nanostructures that cannot be fully quantitated or characterized via conventional physico/chemical analytical tools. Their composition and quality generally depends upon the manufacturing process and controls.

Nanomedicine

The First Nanomedicine generic

- Lipodox, a generic version of Doxil, was the first generic nanomedicine approved by the FDA (2013).
- Lipodox has not been approved by the EMA.

SUN PHARMA



Nanomedicines are complex formulations, and there will always be some degree of polydispersity and batch-to-batch variation. For generic versions, the challenge is to identify meaningful differences between the follow-on and the reference/innovator product.

More Nanomedicine generics are Coming

- Azaya has bioequivalence study underway now with a generic Doxil formulation, ATI-0918.
- Sorrento Therapeutics also has an ongoing bioequivalence study for a nab-paclitaxel alternative IG-001.

AZAYA THERAPEUTICS

SORRENTO THERAPEUTICS

As the number of FDA-approved nanomedicines continues to grow, the importance of developing a framework for evaluation of follow on versions of these treatments becomes increasingly important.

The First Generic Nanodrug

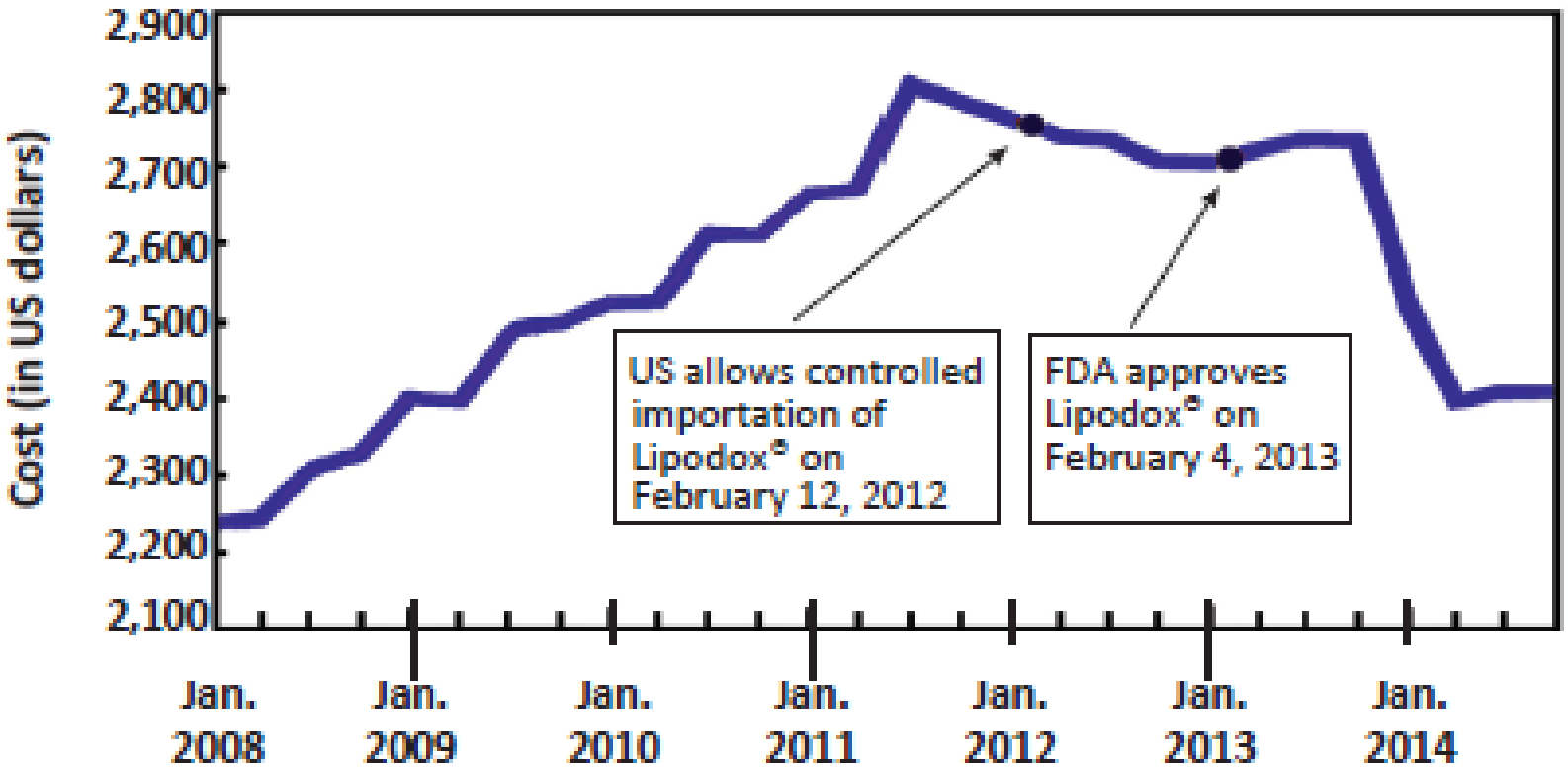


Figure 1.4 Cost for treatment of AIDS-related Kaposi sarcoma (KS) from January 2008 to September 2014.

Source: R. Bawa, 2018

receive premarket regulatory approval. Hence, Lipodox® became the first generic nanodrug (i.e., nanosimilar) approved in the United States. Obviously, this helped alleviate the Doxil® shortage and reduced the cost of care (Fig. 1.4). However, a recent study [11] concluded that *"the data available from this study and in the peer-reviewed literature are compelling suggesting that Lipodox for treatment of recurrent ovarian cancer does not appear to have equal efficacy compared to Doxil. It raises many concerns how to balance the challenges of drug shortages with maintaining the standards for drug approval. A prospective clinical study to compare the two products is warranted before Lipodox can be deemed equivalent substitution for Doxil."*

Smith, J. A., Costales, A. B., Jaff ari, M., Urbauer, D. L., Frumovitz, M., Kutac, C. K., Tran, H., Coleman, R. L. (2016). Is it equivalent? Evaluation of the clinical activity of single agent Lipodox® compared to single agent Doxil® in ovarian cancer treatment. J. Oncol. Pharm. Practice, 22(4), 599–604.

New Drug Application (NDA) or Abbreviated New drug Application (ANDA)?

Pharmacokinetic parameters of 10 mg/kg dose administration paclitaxel formulated in the TPGS-emulsified PLGA NPs *versus* Taxol®.

	Taxol® (i.v.)	Taxol® (oral)	TPGS NPs (oral)
C_{max} (ng/mL)	33,100	103.6	459
$AUC_{(0-t)}$ (ng h/mL)	35,500	872	8510
Sustainable time (h)	21.2	7.02	88.2
Bioavailability (%)		2.46%	24.0%

Lin Mei et al. Pharmaceutical nanotechnology for oral delivery of anticancer drugs. Advanced Drug Delivery Reviews Volume 65, Issue 6, 2013, pages 880 – 890.

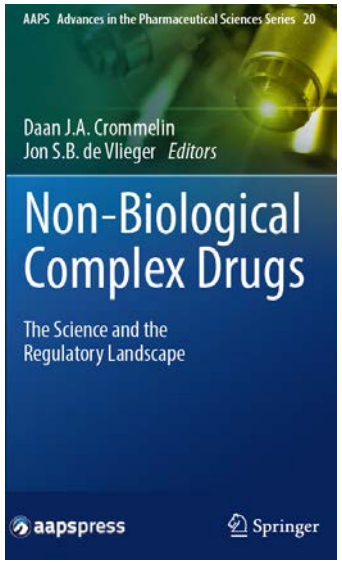
Table 1. Examples of parenteral nanotherapeutic products on the market, including similars if available

Nanotechnology	Active substance	Indication	Brand name originator
Nanocrystals	Olanzapine	Schizophrenia	Zypadhera®
	Paliperidone	Schizophrenia	Xeplion® (EU)/Invega® (US)
Polymeric drugs	Pegaptanib	Wet macular degeneration	Macugen®
	Glatiramer acetate	Multiple sclerosis	Copaxone® (similars available)
Liposomes	Amphotericin B	Fungal infections	AmBisome®
	Cytarabine	Meningeal neoplasms	DepoCyt®
	Bupivacaine	Anesthetic	Exparel®
	Daunorubicin	Cancer-advanced HIV-associated Kaposi's sarcoma	DaunoXome®
	Doxorubicin hydrochloride (PEGylated)	Breast neoplasms; multiple myeloma; ovarian neoplasms; Kaposi's sarcoma	Caelyx® (EU)/ Doxil® (U.S.) (Lipodox®—similar in U.S.)
	Doxorubicin hydrochloride	Breast neoplasms	Myocet®
	Morphine	Pain relief	DepoDur®
	Mifamurtide	Osteosarcoma	Mepact®
	Verteporfin	Macular degeneration, degenerative myopia	Visudyne®
	Vincristine	Philadelphia chromosome–negative acute lymphoblastic leukemia	Marqibo®
Nanoparticles	Aprepitant	Nausea and vomiting	Emend®
	Paclitaxel	Metastatic breast cancer	Abraxane®
	Ferric carboxymaltose	Iron deficiency	Ferinject® (EU)/Injectafer® (U.S.)
	Ferumoxytol	Iron deficiency	Rienso® (EU)/FeraHeme® (U.S.)
	High-molecular-weight iron–dextran	Iron deficiency	Dexferrum®
	Low-molecular-weight iron–dextran	Iron deficiency	Cosmofer®
	Iron gluconate	Iron deficiency	Ferrlecit®
	Iron isomaltoside 1000	Iron deficiency	Monofer®
	Iron sucrose	Iron deficiency	Venofer® (similars available)

What Is a Nonbiologic Complex Drug (NBCD)?

"A medicinal product, not being a biological medicine, where the active substance is not a homomolecular structure, but consists of different (closely) related and often nanoparticulate structures that cannot be isolated and fully quantitated, characterized, and/or described by physicochemical analytical means. It is also unknown which structural elements might affect the therapeutic performance. The composition, quality, and *in vivo* performance of NBCDs are highly dependent on the manufacturing processes of both the active ingredient and the formulation. Examples of NBCDs include liposomes, iron-carbohydrate (iron-sugar) drugs, and glatiramoids."

How do you determine comparability of NBCD follow-on therapeutics?



- Difficult to define an abbreviated procedure for market authorization for NBCDs
- generic or follow-on biologic regulatory guidelines/pathways developed by EMA and FDA to discriminate between biologic drugs and small molecules cannot be extrapolated to NBCDs as they cannot be fully characterized
- Since NBCDs are not fully characterizable or amenable to therapeutic bioequivalence testing, comprehensive regulatory guidelines for follow-on versions of NBCDs are currently not developed
- As many of the NBCDs are also nanomedicines, the requirements for follow-on NBCDs and follow-on nanomedicines are facing the same lack of clarity and need for regulatory pathways.
- US Congress and FDA needs to address this issue to guarantee quality, safety and efficacy of follow-on NBCDs in future - maybe in 2019?

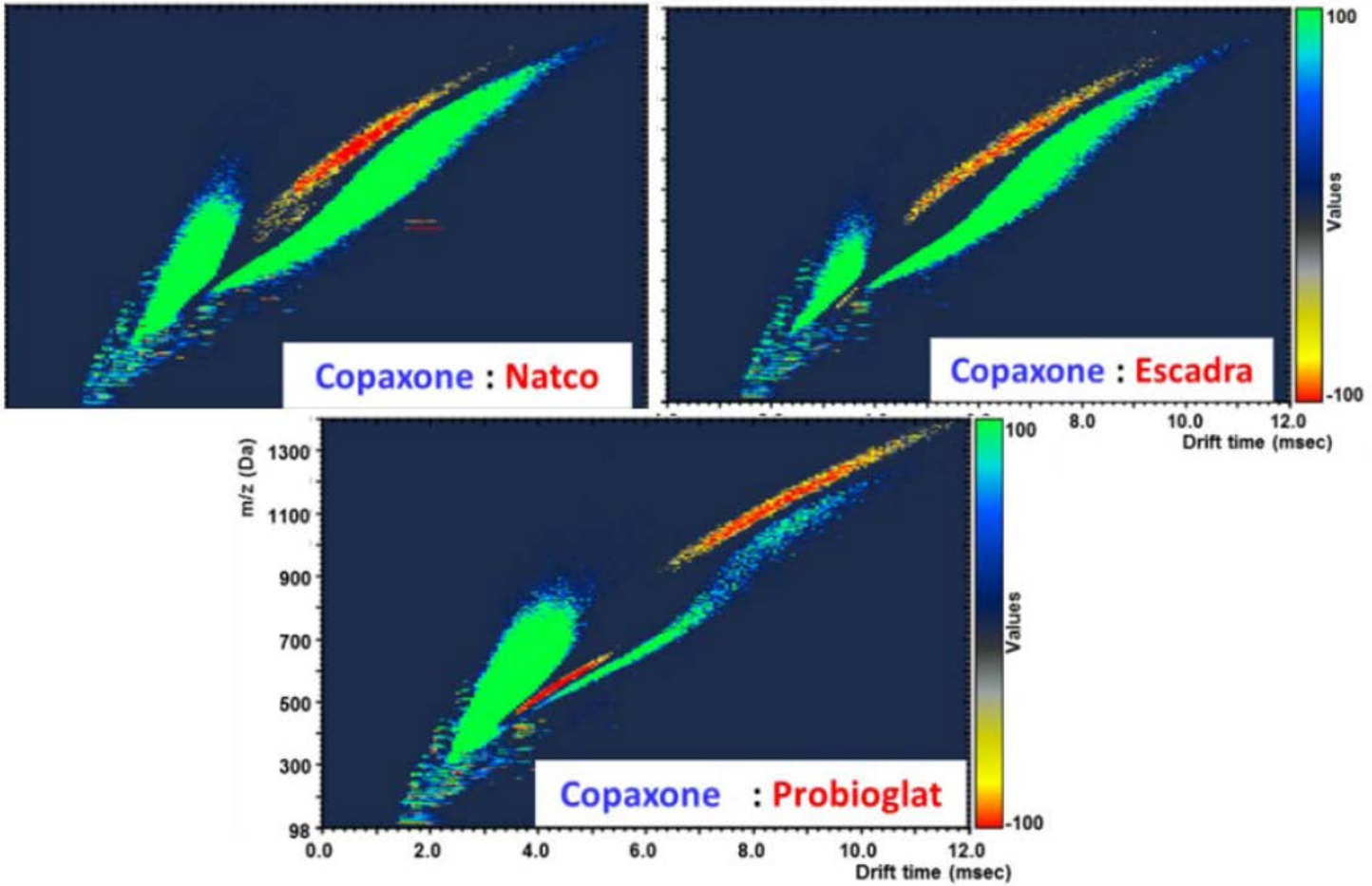


Figure 12: IMMS Heat Map: Copaxone versus Generics

Corresponding Authors: *Dr. Jill B. Conner, Teva Pharmaceutical Industries, Ltd., Specialty Life Cycle Initiatives, Global Specialty Medicines, Overland Park, Kansas, USA; Email: Jill.Conner@tevapharm.com
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Handbook of Clinical Nanomedicine - From Bench to Bedside

www.panstanford.com

Immune Aspects of Biosimilars and Nanosimilars: The Copaxone® Example

It is thus critical to ensure that any proposed follow-on product has a long-term immunogenicity profile that is comparable to Copaxone®'s before approval. This can only be done based upon data from appropriate clinical testing.[17] Surprisingly, despite these immunological concerns, the FDA recently approved so-called generic versions of Copaxone®.

Current Immune Aspects of Biologics and Nanodrugs: An Overview

Raj Bawa, MS, PhD

Patent Law Department, Bawa Biotech LLC, Ashburn, Virginia, USA
The Pharmaceutical Research Institute,
Albany College of Pharmacy and Health Sciences, Albany, New York, USA
Department of Biological Sciences,
Rensselaer Polytechnic Institute, Troy, New York, USA

Lower drug prices, a priority for the Trump Administration, should not supplant patient safety and drug efficacy.

There are enormous pressures on drug regulatory agencies to approve follow-on versions (i.e., generic equivalents) of both biologics and nanodrugs.

Frankly, judging from the rapid pace of biosimilars that were approved in the past year, the Trump administration seems to be pushing for an increase in biosimilar approvals at the FDA.

Concurrently, the increase in the number of drug companies targeting generic opportunities and seeking US market exclusivity for generic versions of major branded products is on the rise.

Owing to the complexity of NBCDs and nanodrugs, showing equivalence is more challenging for their follow-on versions. Therefore, the interchangeability or substitutability of nanosimilars and their listed reference product(s) cannot be taken for granted.

In the past, nanosimilars have been approved via generic pathways but differences in clinical efficacy and safety have been reported in the scientific literature following approval

Table 1.6 Standard industry immunogenicity prediction tools and models

In silico	*In vitro*	*In vivo*
iTope™ TCED™ Epibase® EpiMatrix™	EpiScreen™—*Ex vivo* assessment of immunogenicity ➢ EpiScreen™ time course T cell assay ➢ EpiScreen™ DC:T cell assay ➢ EpiScreen™ T Cell Epitope Mapping ➢ EpiScreen™ MAPPS—MHC Class II—Associated Peptide Proteomics Epibase® REVEAL®	conventional mouse models immune-tolerant transgenic mice HLA-immune-tolerant transgenic mice nonhuman primate models

Abbreviations: DCs, dendritic cells; MHC, Major Histocompatibility Complex; MAPPS, MHC Class II Associated Peptide Proteomics; TCED™, T Cell Epitope Database; HLA, human leukocyte antigen.

Note: Although these tests are widely used for biologic immunogenicity prediction, they could pertain to both biologics and nanodrugs because of considerable overlap in their definitions (Sections 1.2 and 1.3).

Table 1.7 Recommendations to the FDA for faster development and licensing of biosimilar products[14]

• The FDA should remove the current default requirements of conducting bridging studies between a US-licensed product and a non-US approved comparator to establish biosimilarity.
• The FDA should present clear and open scientific views to the public, more particularly, to the prescribers that a biosimilar product has "no clinically meaningful difference" from the originator product and thus suitable for naïve patients.
• The FDA should encourage the development of *in vitro* immunogenicity testing methods to reduce exposure of test subjects on ethical grounds.
• The FDA should revise some of the specific statistical testing methodologies in establishing analytical similarity to remove certain contradictions in the guidance.
• The FDA should take a fresh look at the clinical relevance of the protocols and statistical methods used to establish PK/PD similarity, and to make these studies more clinically relevant while reducing their cost.

[14]Based on the Citizen Petition (CP) of Dr. S. K. Niazi of the University of Illinois College of Pharmacy to the FDA (dated May 11, 2018; docket number FDA-2018-P-1876) that focuses on reducing human testing to establish bioequivalence. It was accepted by the FDA and as of June 2018 was under the comment period. In the past, I have filed CPs on behalf of Teva pertaining to Copaxone®.

"Institutional corruption is a normative concept of growing importance that embodies the systemic dependencies and informal practices that distort an institution's societal mission. An extensive range of studies and lawsuits already documents strategies by which pharmaceutical companies hide, ignore, or misrepresent evidence about new drugs; distort the medical literature; and misrepresent products to prescribing physicians... First, through large-scale lobbying and political contributions, the pharmaceutical industry has influenced Congress to pass legislation that has compromised the mission of the Food and Drug Administration (FDA). Second, largely as a result of industry pressure, Congress has underfunded FDA enforcement capacities since 1906, and turning to industry-paid "user fees" since 1992 has biased funding to limit the FDA's ability to protect the public from serious adverse reactions to drugs that have few offsetting advantages. Finally, industry has commercialized the role of physicians and undermined their position as independent, trusted advisers to patients."

Light, D. W., Lexchin, J., Darrow, J. J. (2013). Institutional corruption of pharmaceuticals and the myth of safe and effective drugs. *J. Law Med. Ethics*, **14**(3), 590–610.

I am not a fan of the various accelerated approaches currently underway and on the rise at global regulatory agencies, primarily at the FDA, EMA, and PMDA. For serious or life-threatening disease, the FDA can approve drugs through its accelerated approval review track based on surrogate end-points (rather than hard clinical end-points) that are "reasonably likely to predict clinical benefit." This pathway was designed in the early 1990s to speed drug development. Various accelerated approaches include breakthrough therapy designation, accelerated approval, and conditional marketing authorization—collectively referred to as "facilitated regulated pathways" (FRPs). A greater uncertainty is introduced into the regulatory approval process via FRPs. This could translate into unwanted immunogenicity.

In future, drug companies will need to increasingly prove to regulators that neither their manufacturing processes nor later use of the final drug product generates CARPA, immunogenicity, ADAs, or ICs in a manner that causes adverse reactions impacting safety or efficacy. Regulatory agencies must hold biologics and nanodrugs to strict safety and efficacy standards now so that corresponding follow-on versions later (biosimilars, nanosimilars, NBCD similars are also safe and efficacious.

“[W]ith respect to drugs, there is no substitute for a well-controlled clinical trial to establish a drug’s safety and effectiveness and conducting such a trial is beyond the competence of individual consumers. Consumers, unprotected by regulations requiring such trials, are unable to judge the safety and effectiveness of a drug…Nevertheless, the regulatory framework is unsettled and there are now, as there have been in the past, demands in Congress and elsewhere to change the laws under which FDA operates.”

Tyler, R. S. (2013). The goals of FDA regulation and the challenges of meeting them. Health Matrix, 22(2), 423–431:

"Problems in clinical studies are an indication of missed opportunities to successfully define the real-world effectiveness and safety of drugs. Driven largely by commercial interests, many clinical studies generate more noise than meaningful evidence to guide clinical decision making. Greater involvement of nonconflicted bodies is needed in the design and conduct of clinical studies, along with more head-to-head comparisons, representative patient populations, hard clinical outcomes, and appropriate analytical approaches. Documenting, registering, and publishing study protocols at the outset and sharing participant-level data at study completion would help ensure transparency and enhance public trust in the clinical research enterprise. Such an approach is needed to generate evidence that is better suited to the tasks of predicting the clinical utility of drugs and providing the information needed by patients and clinicians. Future efforts

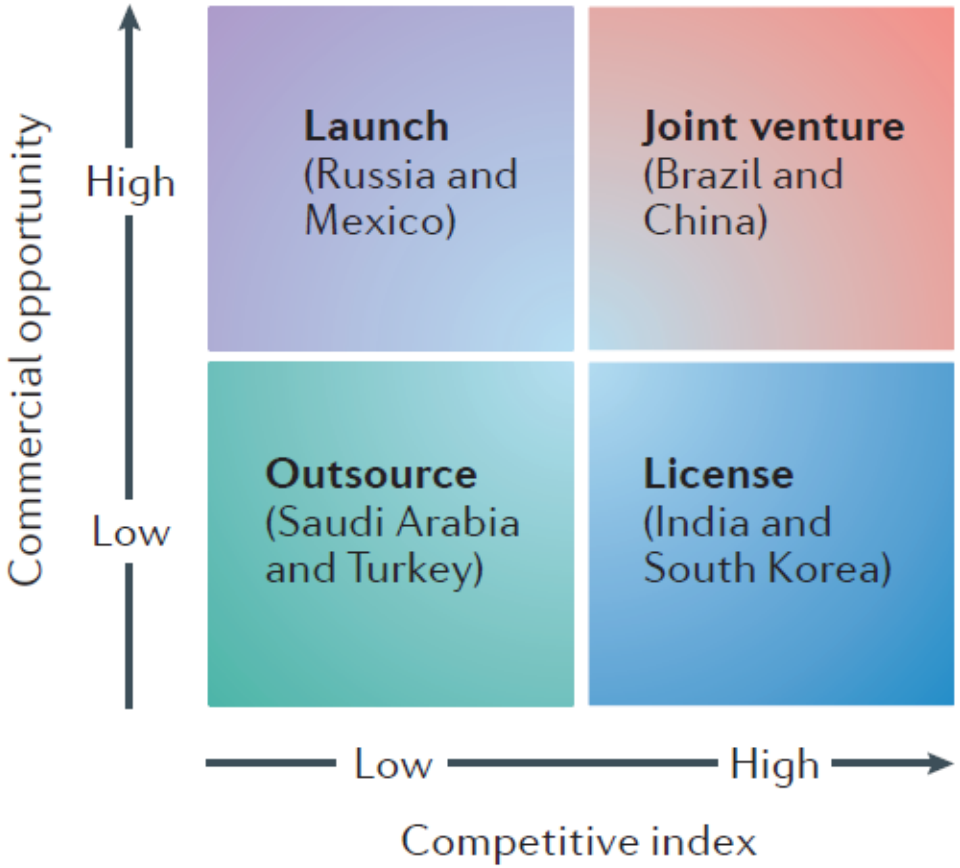


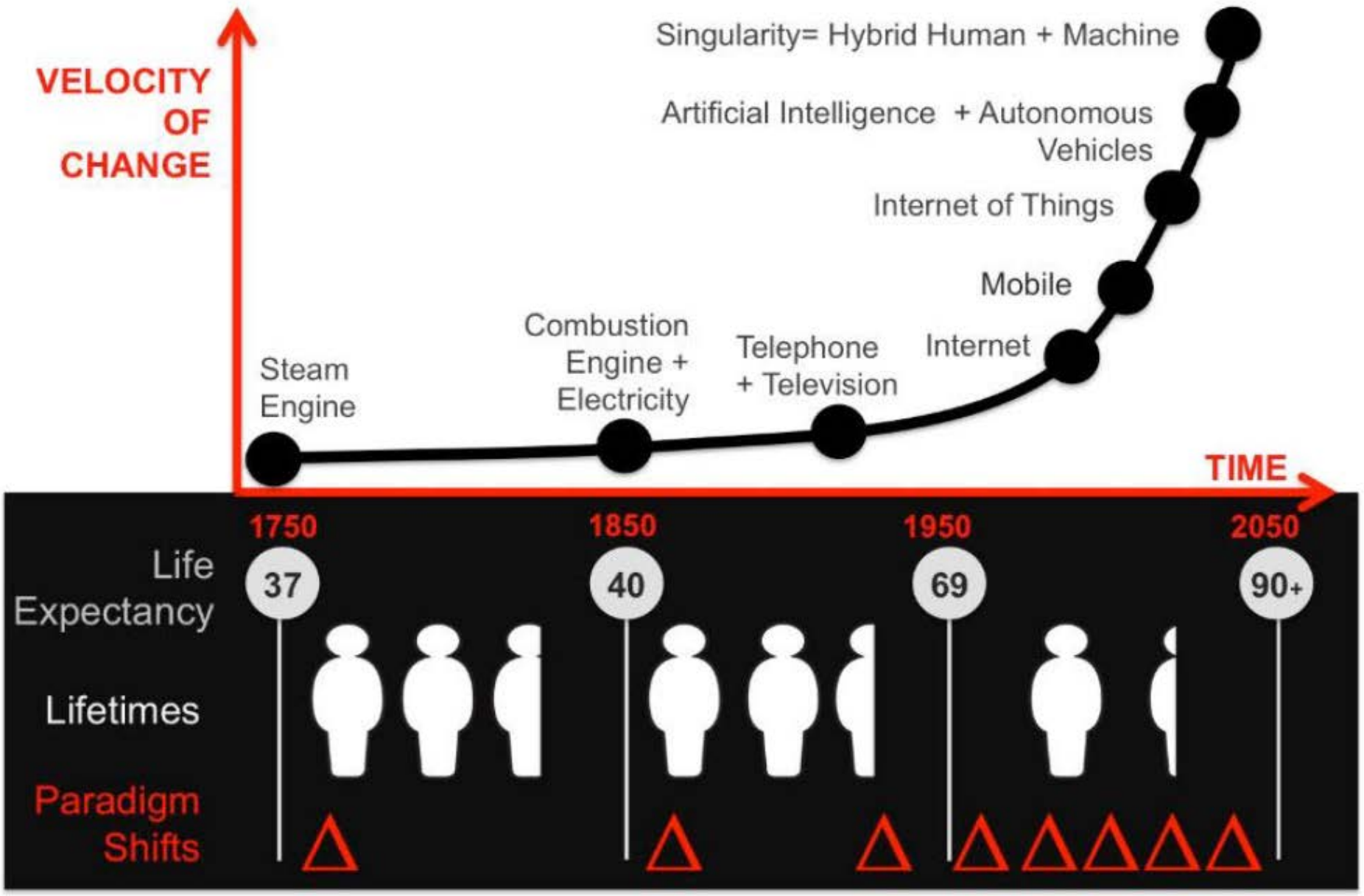
Figure 1 | **Classification of strategies for biosimilars in emerging markets.** The commercial opportunity and an accessibility index were used to assign the eight countries shown into one of the four cells shown in the 2 × 2 matrix, based on whether the market potential and competitive index score for that country was above or below the median value for the group of countries overall. See

Executive summary

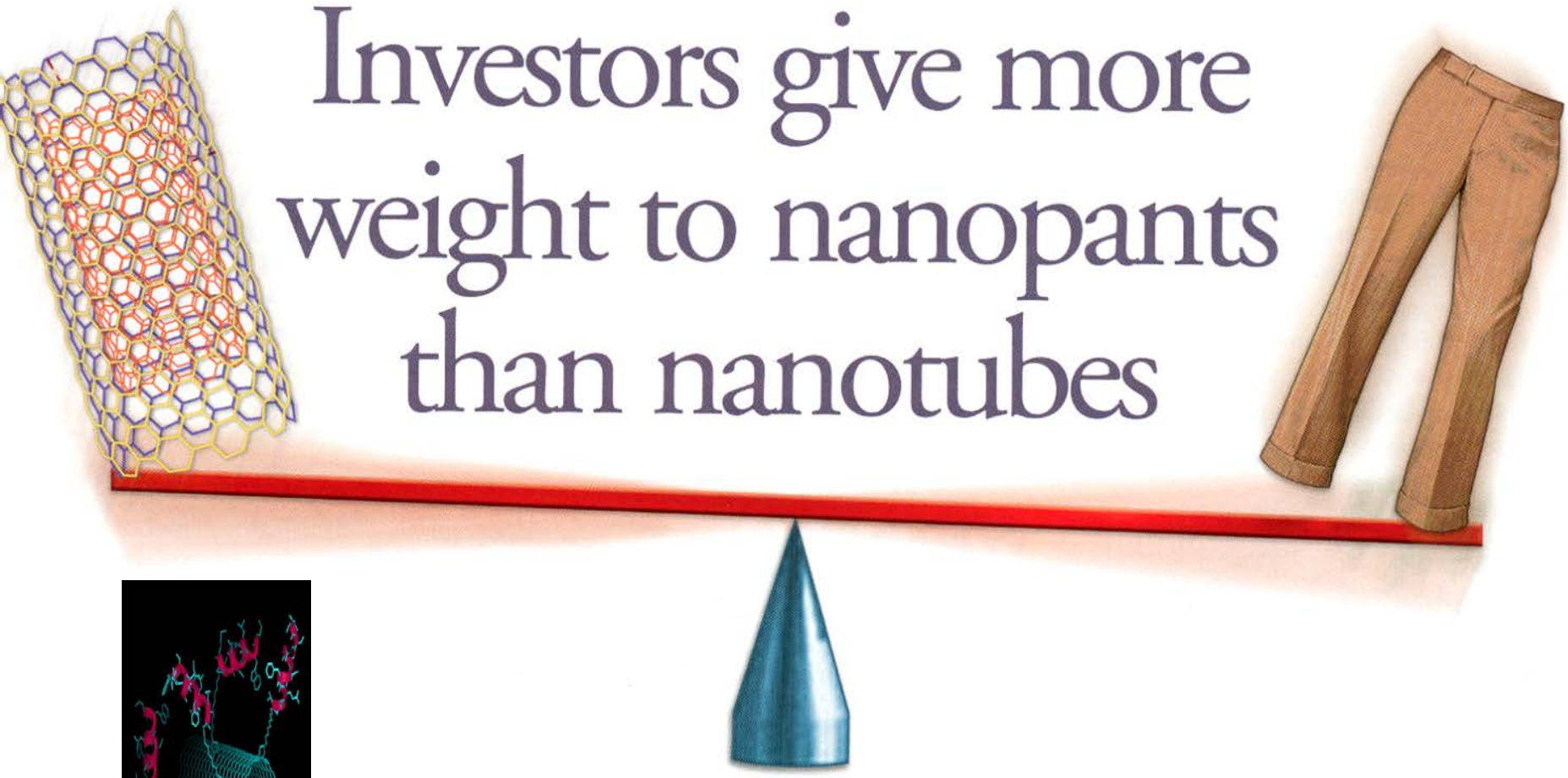
- First-generation nanomedicines have been clinically established as successful medicines.
- The number of marketed pharmaceuticals using nanotechnology is expected to continuously grow and, thus, will benefit patients and public health.
- Drug regulators need to ensure:
  - The safe market introduction of nanosimilars (i.e., 'follow-on' nanomedicine products);
  - That next-/second-generation nanomedicines enter clinical development and, consequently, the market in a safe and timely way for the benefit of public health.
- Recent European Medicines Agency initiatives to facilitate the development of nanomedicines include:
  - Publication of a reflection paper on block copolymer micelles, liposomal products and nanosized colloidal iron-based preparations;
  - Organization of the first international workshop on Nanomedicine Regulation in collaboration with other agencies (e.g., US FDA and the regulatory authorities of Canada, Japan and Australia).


The Future...

Velocity of Change Requires Adaptation



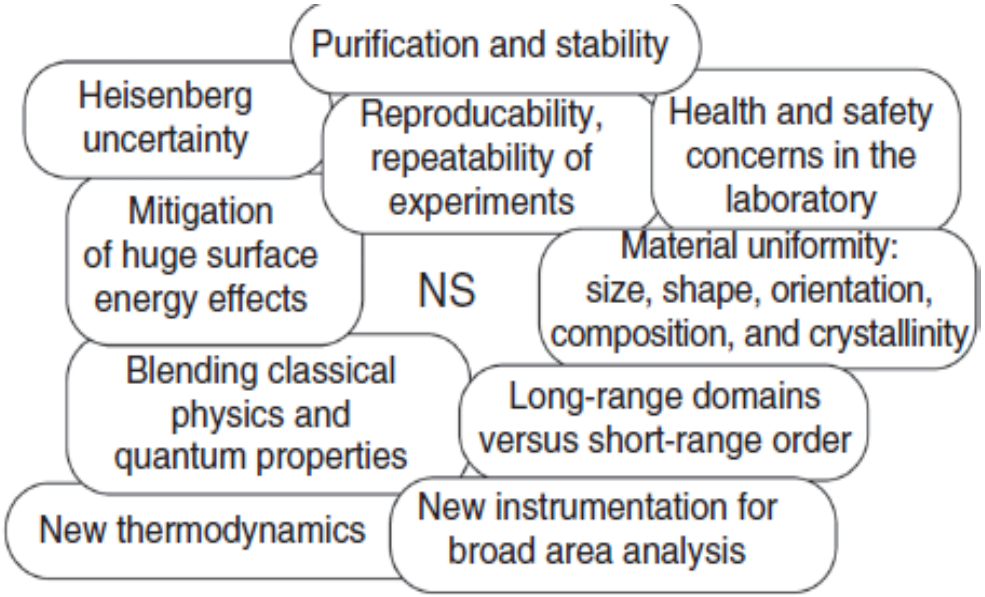
What is the Reality?

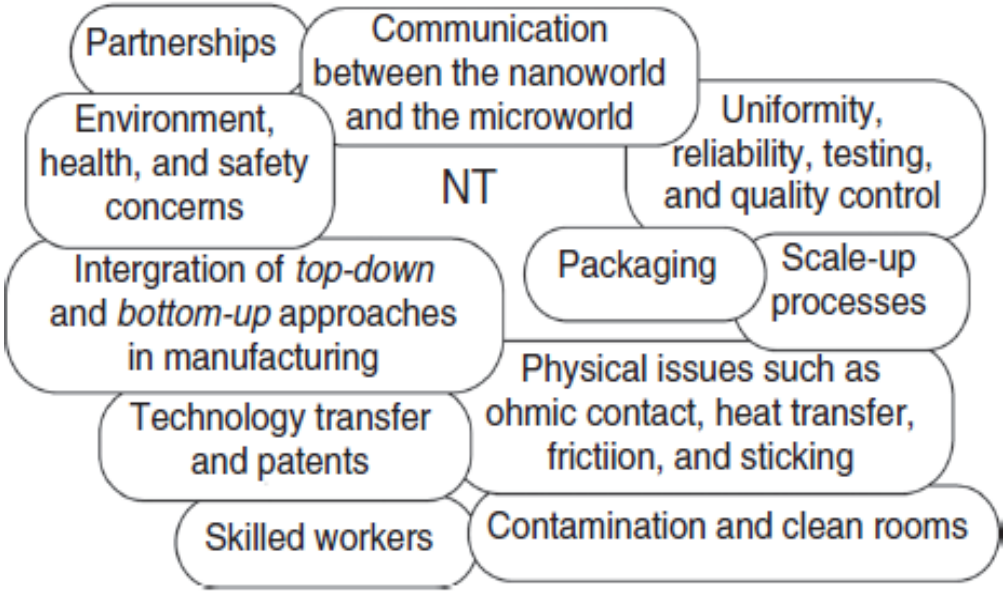


Courtesy: *Small Times*

What are the problems?

"Commercial nanotechnology is at a nascent stage. Large-scale production challenges, high production cost, the public's general reluctance to embrace innovative technology without real safety data or products, and a well-established micron-scale industry are just a few of the bottlenecks facing early-stage nanotechnology commercialization."





R. Bawa (2004). ***Nanotechnology Law and Business*** **1(1):31-50.**

What are the societal and ethical consequences?

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The Ethical Dimensions of Nanomedicine

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Is due diligence critical for commercialization? Get out the patent microscope

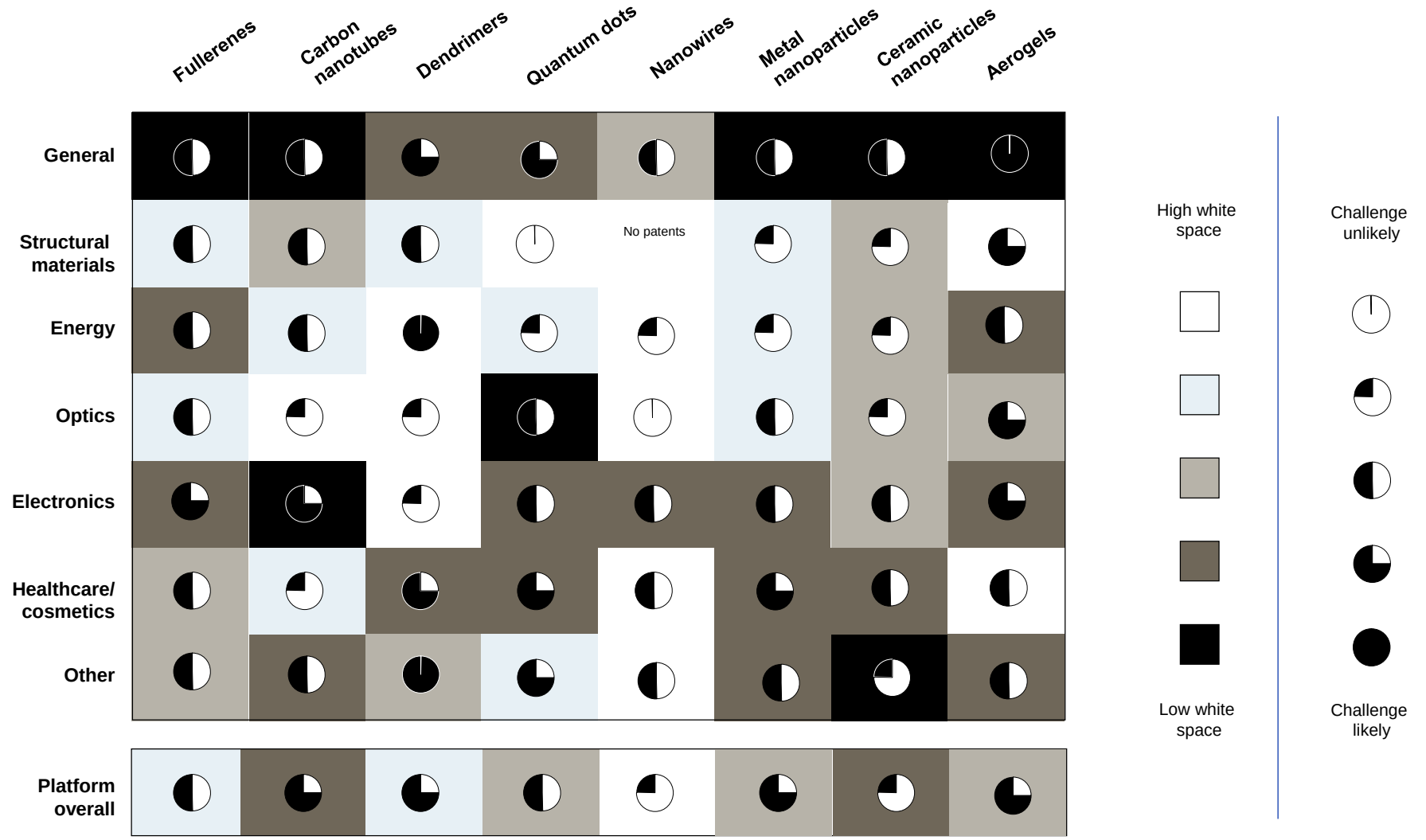
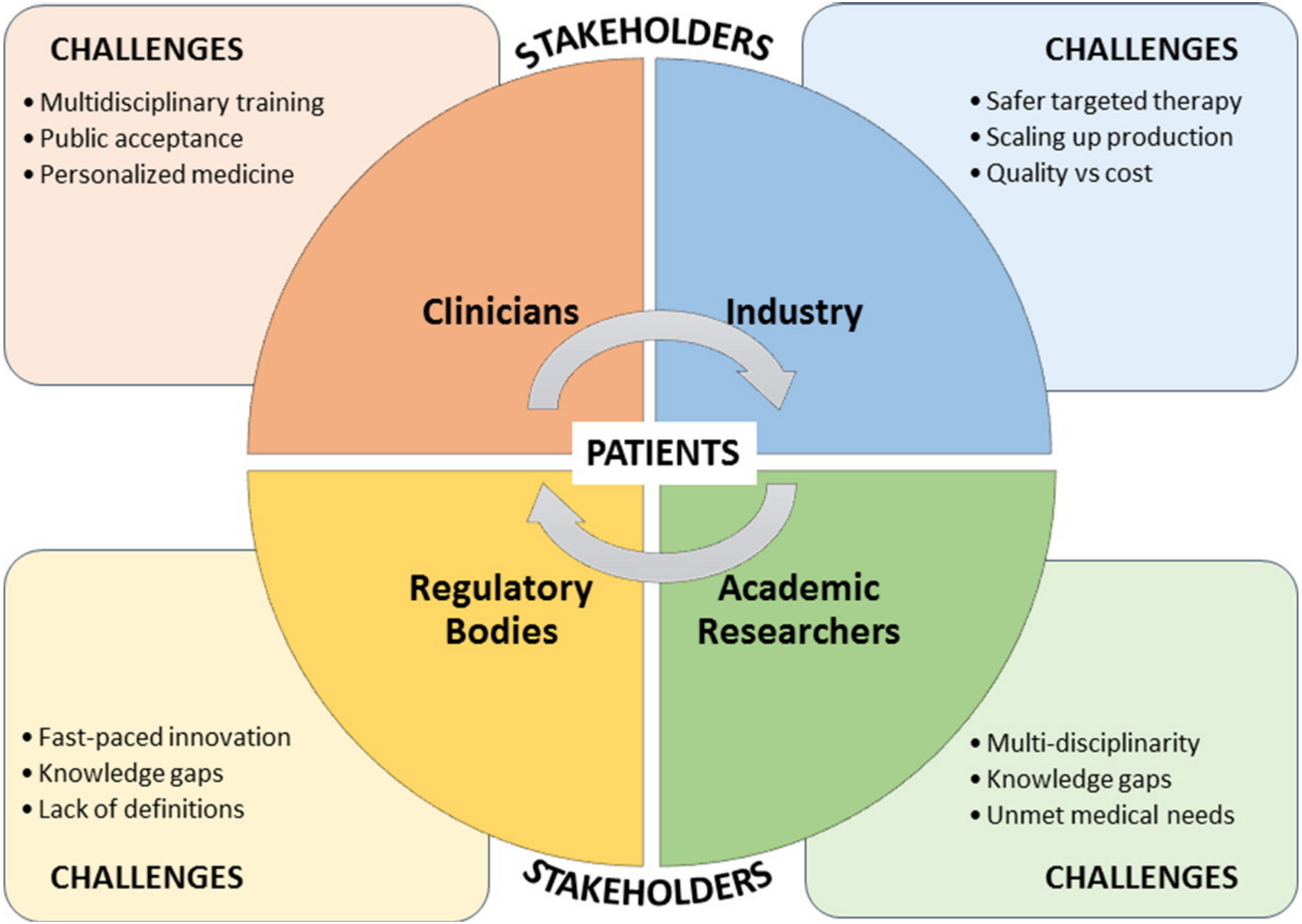


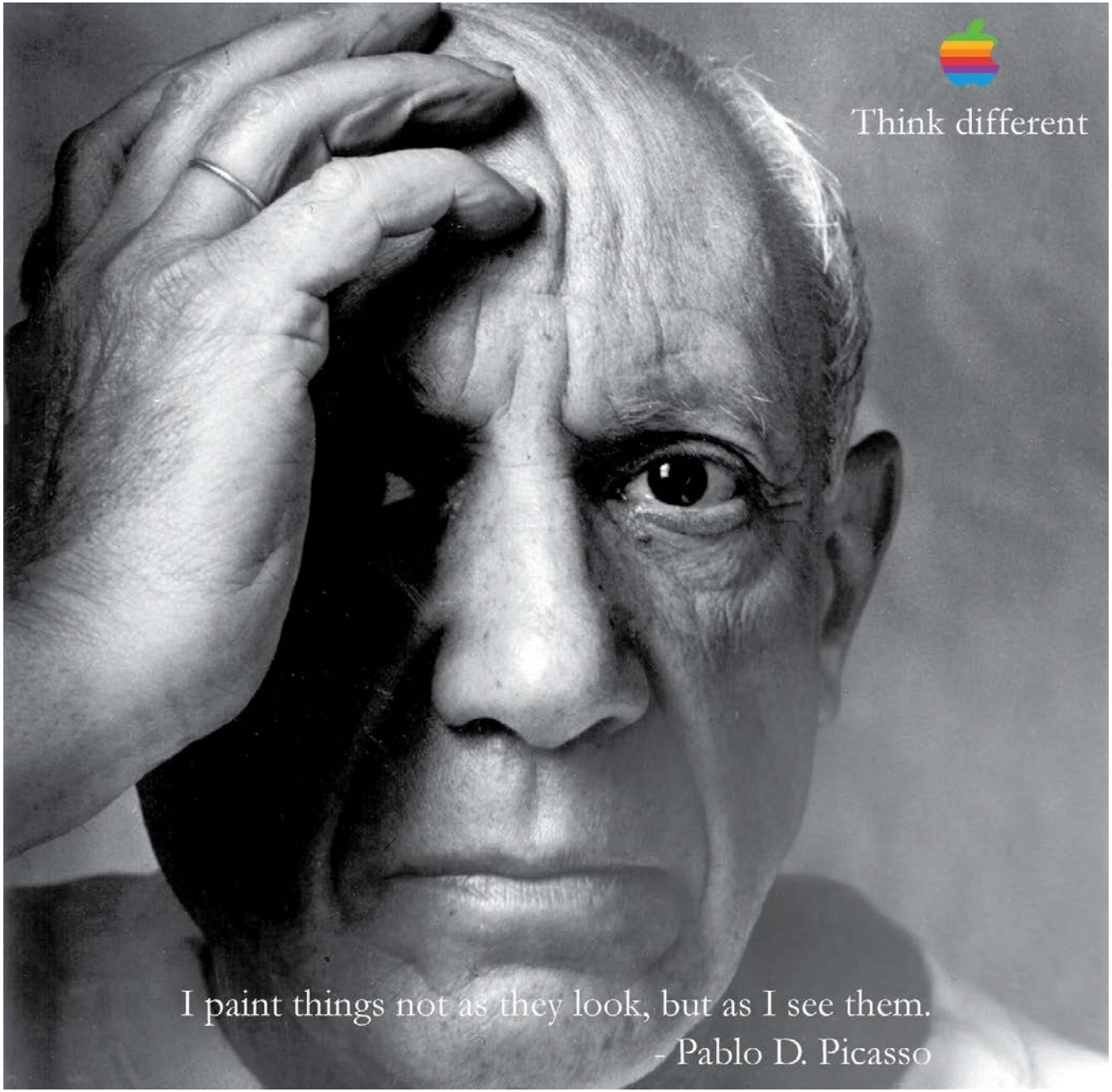
Fig 2 US patent thicket analysis by nanomaterial technology sector. (Courtesy of Lux Research, New York, NY, and Foley Lardner, Washington, DC).

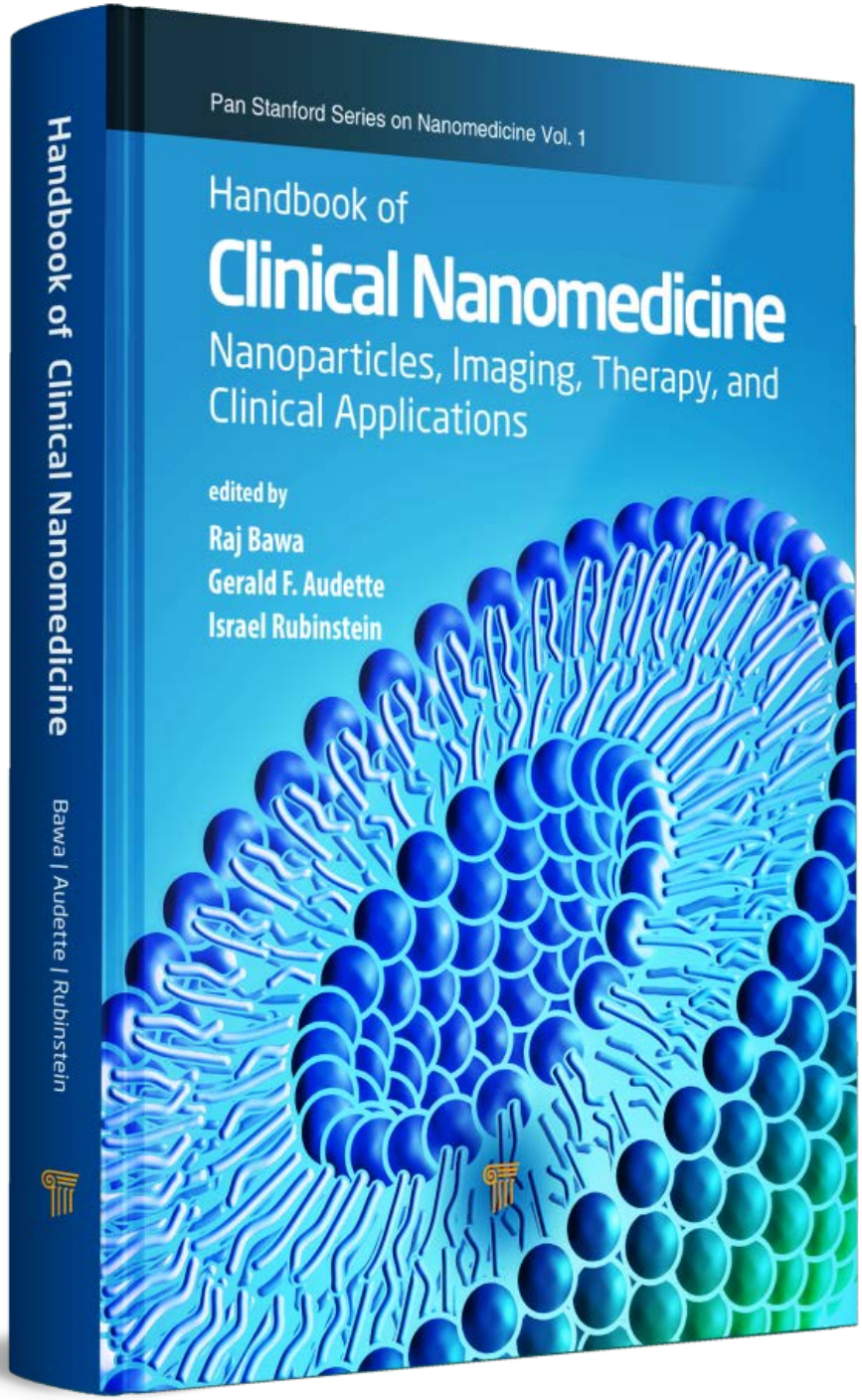
R. Bawa. Nanomedicine: Nanotechnology, Biology and Medicine Volume 1, Issue 4, 2005 346 - 350

What are the best models?



Do we need to think outside the box?

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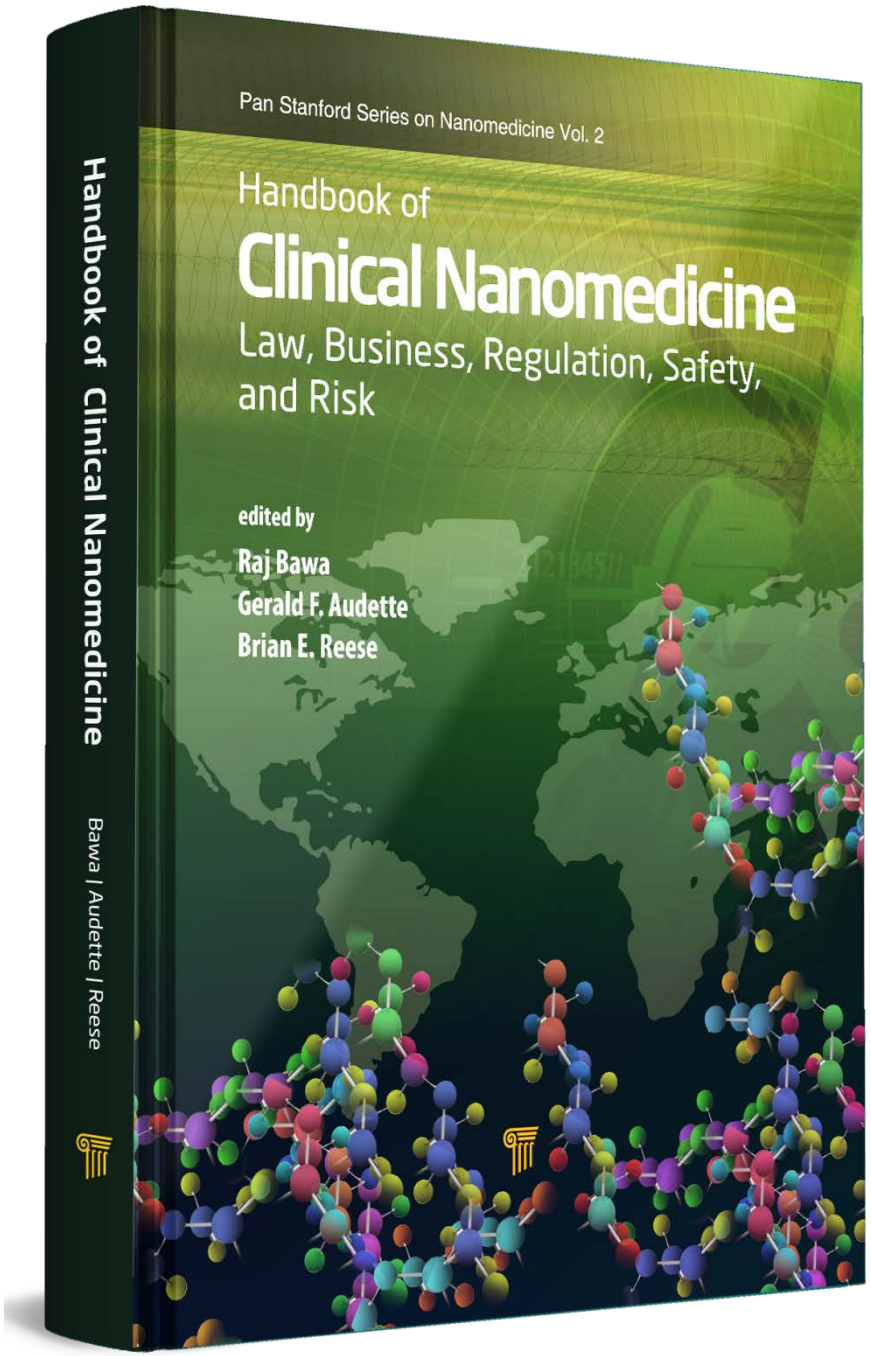
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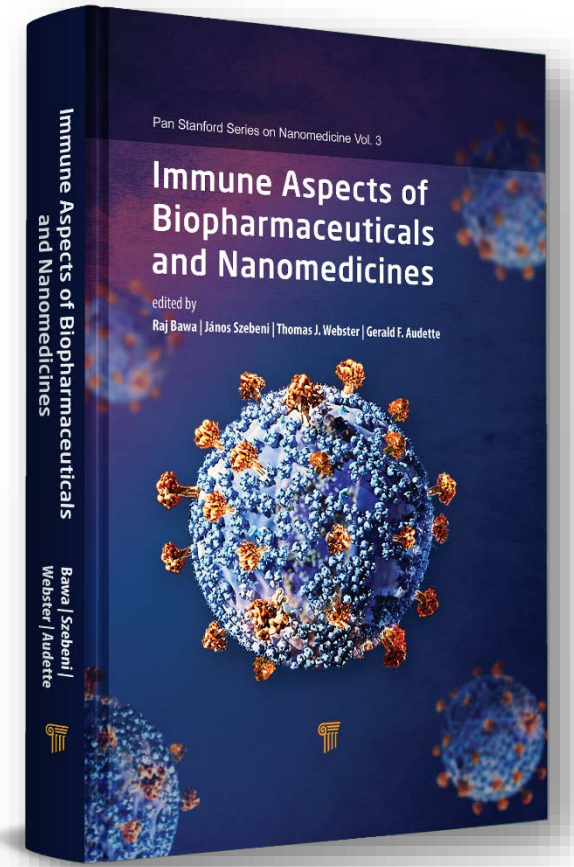

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Questions

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