The Current Status of Nanomedicine in the USA in Comparison to the Rest of the World

Committee Meeting on the National Nanotechnology Initiative: A Quadrennial Review (NNI) May 22-23, 2019.

COI: IP developed by Nel et al was licensed to Westwood Bioscience and NAMMI Therapeutics by The Regents of UC. AN is co-founder, equity holder, and SAB chair of Westwood Bioscience, Inc and NAMMI Therapeutics.

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Research DIirector California NanoSystems Institute
Director UC Center for the Environmental Implications of Nanotechnology
Associate Editor ACS Nano

Quadrennial Review of the National Nanotechnology Initiative

Project Scope:

The NRC will appoint an ad hoc committee to conduct the quadrennial review of the National Nanotechnology Initiative (NNI). The overall objective of this review is to make recommendations to the Nanoscale Science, Engineering, and Technology (NSET) Subcommittee of the White House National Science and Technology Council and to the National Nanotechnology Coordination Office that will improve the value of the NNI's research and development strategy and portfolio to the economic prosperity and national security of the United States. Toward this objective, this quadrennial NNI review will include the following tasks:

A. Analyze the relative position of the United States compared to other nations with respect to nanotechnology research and development, including trends and developments in nanotechnology science and engineering and the identification of any critical research areas where the United States should be the world leader to best achieve the goals of the Program;

B. Assess the current state of nanoscience and nanotechnology resulting from the NNI as authorized in 2003, including the current impact of nanotechnology on U.S. economic prosperity and national security. Based on this assessment, consider if and how the NNI should continue. If continuation is suggested, make recommendations regarding new or revised Program goals, new research areas and technical priorities, partnerships, coordination and management mechanisms, or programs to be established to achieve these goals.

What is Nanomedicine?

Nano2 (2010): Nanotechnology Research Directions for Societal Needs in 2020

"The design and synthesis of biologically interactive nanoscale systems that enable medicinal technology advances in:

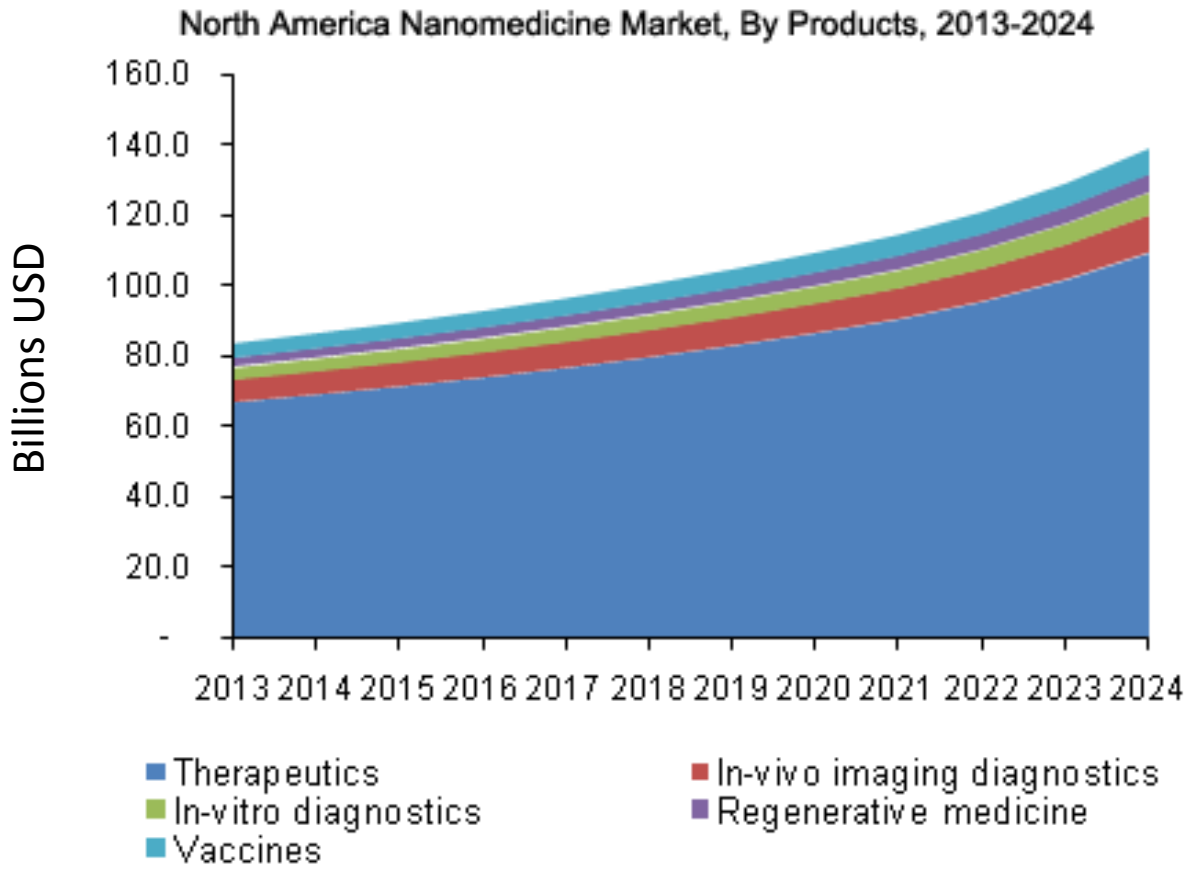
- **Prevention, diagnostics, treatment of diseases, including personalized, point-of-care modalities**
- **Preservation and improvement of human health**
- **Chronic and acute pain relief**

by leveraging significant advantages nano-systems hold over traditional methods of sensing, imaging, reconstruction, delivery and interaction with biological systems"

Current, Pragmatic Definition of Nanotherapeutics

Use of therapeutic or imaging agents that make use of nanoparticles and nanodevices to control the biodistribution, enhance the efficacy or reduce the toxicity of a drug or biological agents

North America Nanomedicine Market (by products), 20013-2024



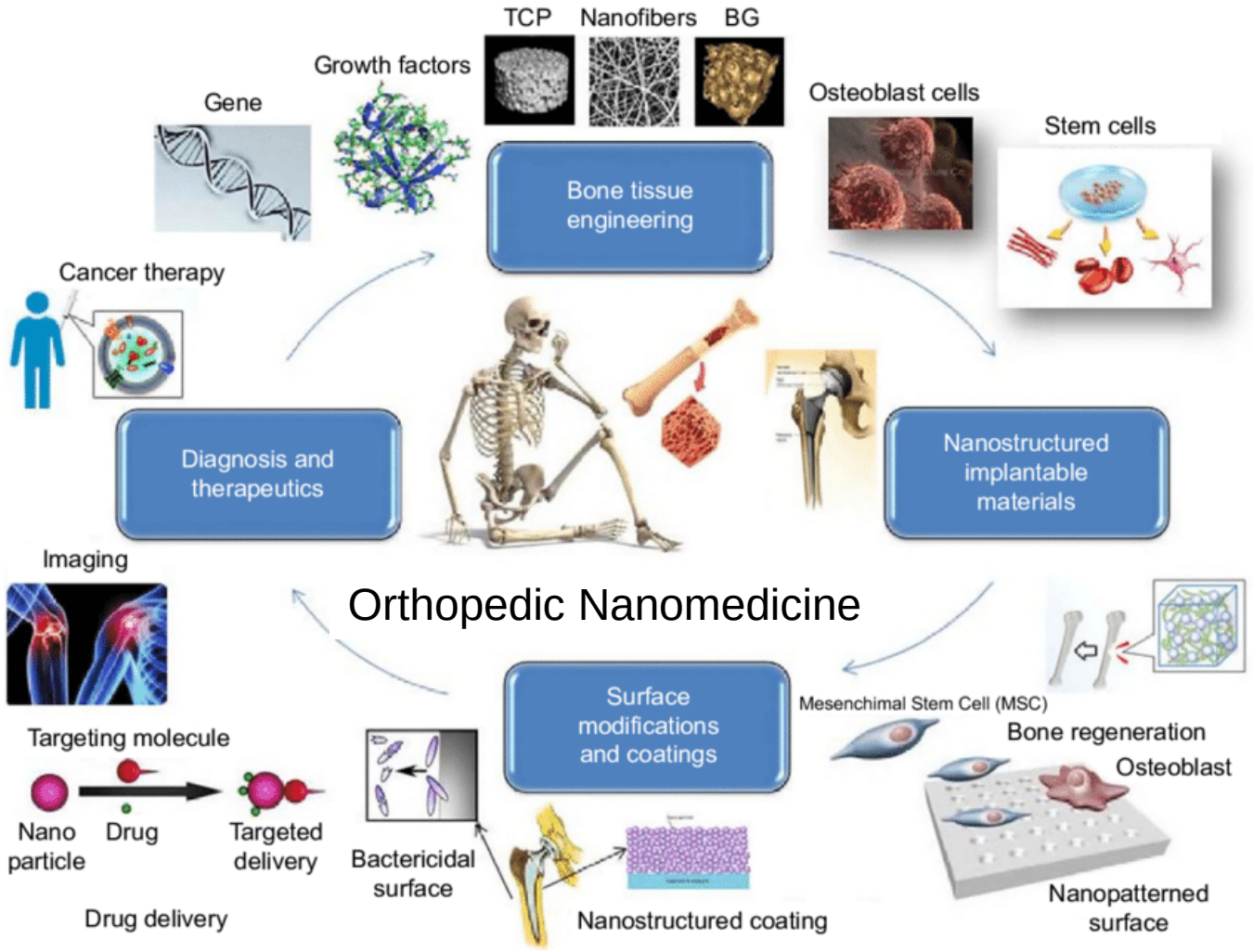
Market research scope

Attribute	Details
Base year used for market estimation	2015
Historic Analysis	Actual data from 2013 to 2015
Forecast	2016 to 2024

https://globalmarketresearchinsight.wordpress.com/tag/nanomedicine-market/

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

Nanomedicine is Key Driver of US Competitiveness in Nano



International Journal of Nanomedicine 2015:10 6039–6054

- Cancer
- Neurology
- Cardiovascular
- Infectious disease
- Immunology: vaccines, tumors
- Anti-inflammatory/Aging
- Regenerative/Rehabilitation
- Orthopedics

- Engineered Approach to Medicine
- Unconquered disease
- Personalized Medicine
- Nanosensors/imaging
- Preventative
- Regenerative
- Remote (tele) medicine

Status of Current Nanotherapeutics

- Most are “simple” nanoparticles/material compositions (e.g., liposomes, polymers)
- Deliver mostly conventional drugs that have been prior approved and used
- Dozens of nanodrugs received FDA approval and 77 are in clinical trials (2016)
- Hundreds of therapeutic nanoparticles are in early stage development
- Structure-activity relationships (e.g., size, charge, shape, composition, architectures) still evolving and adapted to disease requirements
- Broadening of particle types and multifunctional features will increase the scope and complexity of future nanotherapeutics
- Use of the intrinsic material properties for therapeutic purposes is evolving (e.g., surface architectures for regenerative medicine)

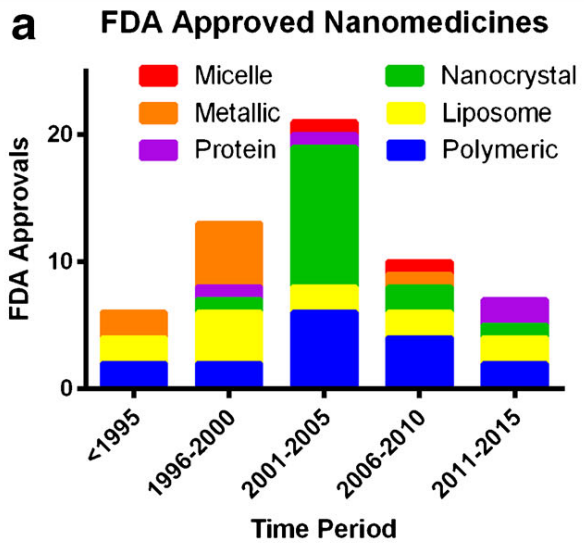
Recent Published Survey of ClinicalTrials.gov

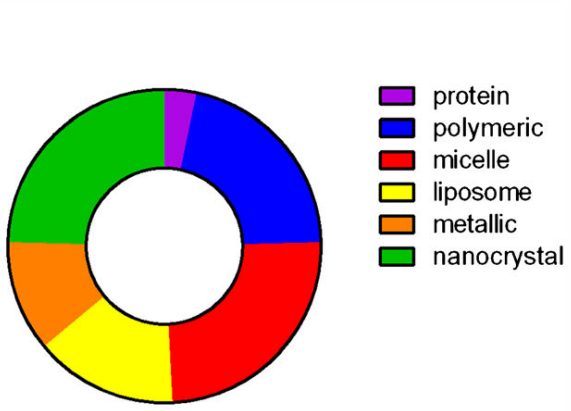
Average of 13 nanomedicines per 5 yr period since 1995

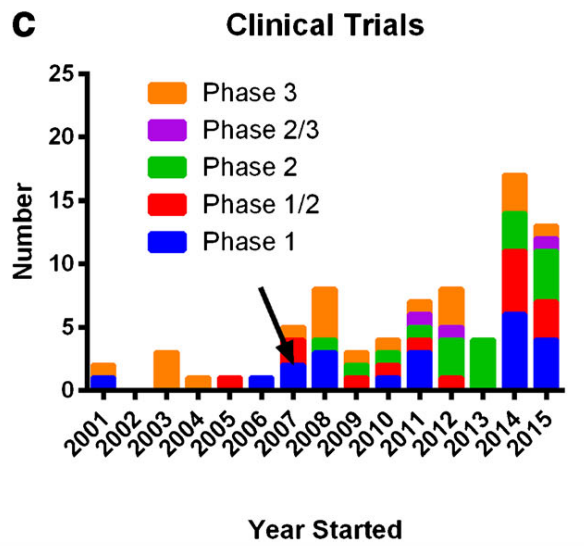
Increasing IND approvals for clinical trials since 2007

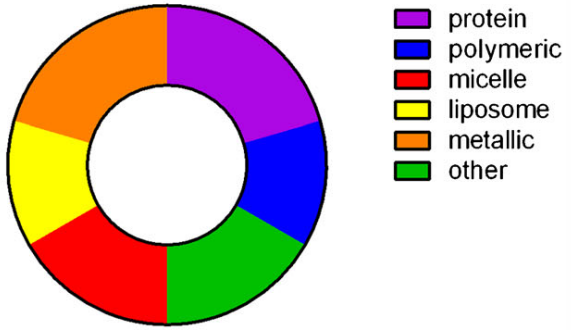
Liposomes and polymeric NPs joined by micelles, metallic and protein based NPs

We will see the critical mass of these efforts soon?









Bobo et al. Pharm Res (2016) 33:2373–2387

frontiers in Pharmacology

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

Nanomaterial Medicine Formulations currently approved for Marketing

Type	Name	Drug	Indication
Liposomal NNMs	Doxil/Caelyx	Doxorubicin	HIV-related Kaposi's Sarcoma, metastatic breast cancer, advanced ovarian cancer, multiple myeloma
	AmBisome	Amphotericin B	Fungal infections
	DaunoXome	Daunorubicin	HIV-related Kaposi's Sarcoma
	Myocet	Doxorubicin	Metastatic breast cancer
	Abelcet	Amphotericin B	Fungal infections
	Lipo-Dox	Doxorubicin	HIV-related Kaposi's Sarcoma, ovarian cancer, multiple myeloma
	Marqibo (Onco-TCS)	Vincristine	Adult AML
	Onivyde	Irinotecan	Pancreatic cancer
	Vyxeos (CPX-351)	Cytarabine and daunorubicin	AML
	Visudyne	Verteporfin	Wet AMD, myopia, ocular histoplasmosis
	DepoDur	Morphine	Postoperative analgesia
	DepoCyt	Cytarabine	Lymphomatous meningitis
Micellar NNMs	Genexol PM	Paclitaxel	Metastatic breast cancer, advanced lung cancer
	Nanoxel M	Paclitaxel	Advanced NSCLC, breast cancer, pancreatic cancer, ovarian cancer
Protein NNMs	Abraxane	Paclitaxel	Breast cancer, NSCLC, pancreatic cancer

(Ref: ema.europa.eu; drugs.com; fda.gov).

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Global Workforce Distribution in Nanomedicine (2016)

Academia	Industry	Clinic / public health
61 %	21 %	18 %

If the expected growth in the marketplace is going to be realized, the 2016 statics will change drastically with an expected big gain in Industry and the Clinic.

From Academia we expect many spin-offs and small start up companies.

Dr. med. h.c. Beat Löffler MA, CEO
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Major Players in the Global Nanomedicine Market

- Merck & Co. Inc.
- Hoffmann-La Roche Ltd.
- Gilead Sciences Inc.
- Novartis AG
- Amgen Inc.
- Pfizer Inc.
- Eli Lilly and Company
- BASF SE
- Johnson & Johnson
- Abbott Laboratories
- GlaxoSmithKline plc
- Bristol-Myers Squibb Co
- GE Healthcare
- Nanobiotix SA
- Sanofi
- UCB SA
- Shimadzu Co. Ltd

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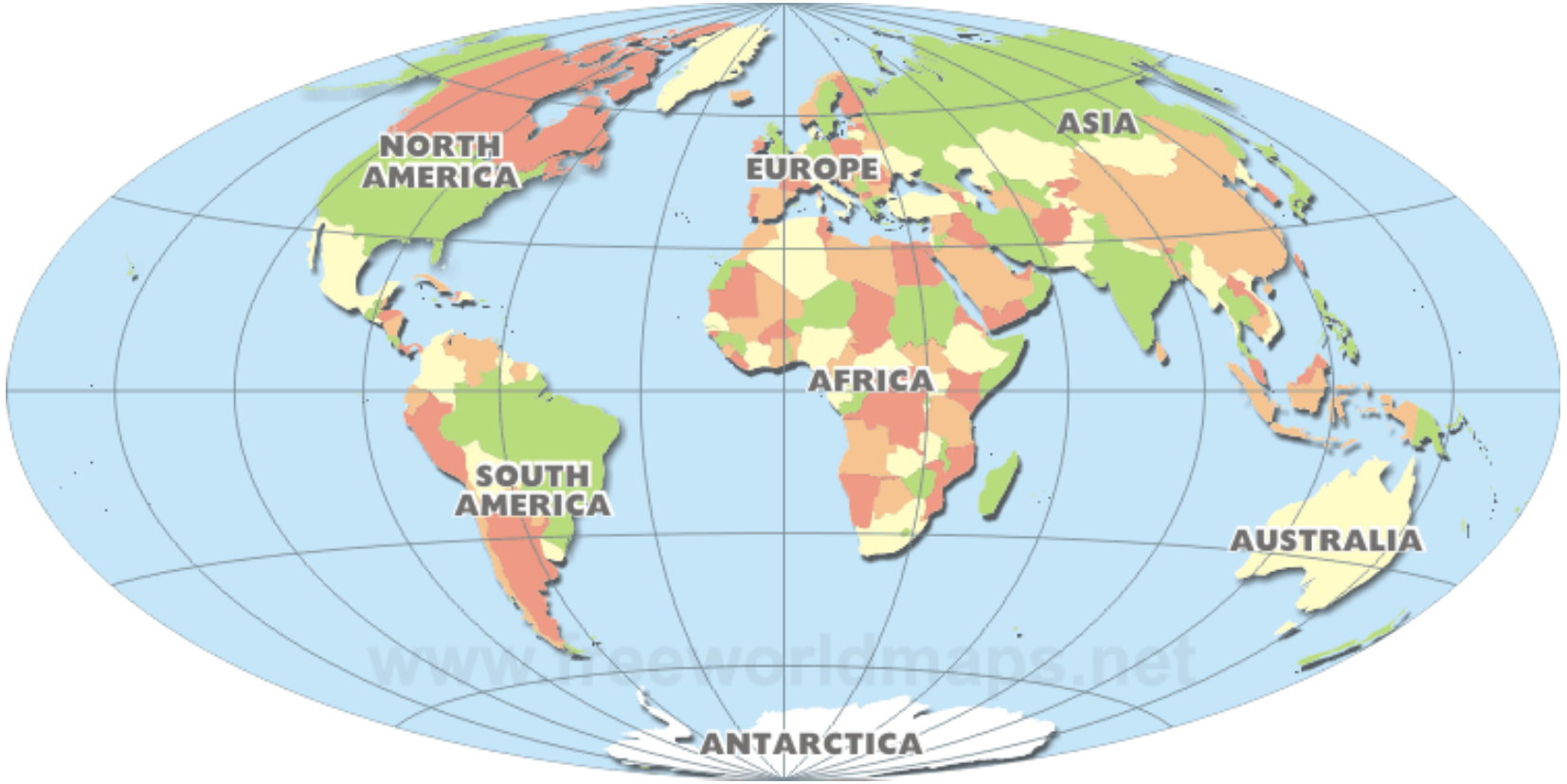
Nanomedicine Market July 2018 by Regions



USA / CANADA	EUROPE	ASIA (& JAPAN)	LATIN AMERICA	AFRICA (& ME)	AUSTRALIA (& NEW ZEALAND)
42%	24%	21%	5%	4%	4%

Adapted from: Dr. med. h.c. Beat Löffler MA, CEO

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Fastest Growing Market: Asia Pacific

Largest Market: North America

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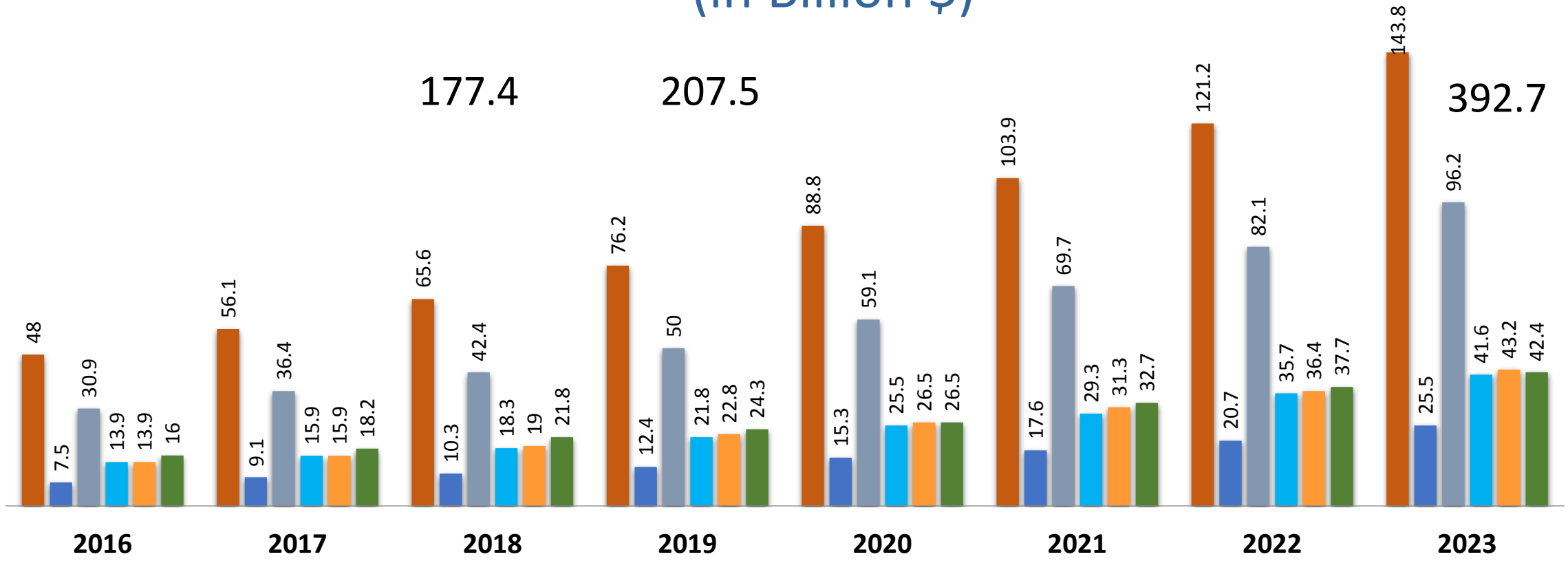
Global Nanomedicine Market Revenue by Application Type (in Billion $)



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Source: Infoholics Report Dec. 2017

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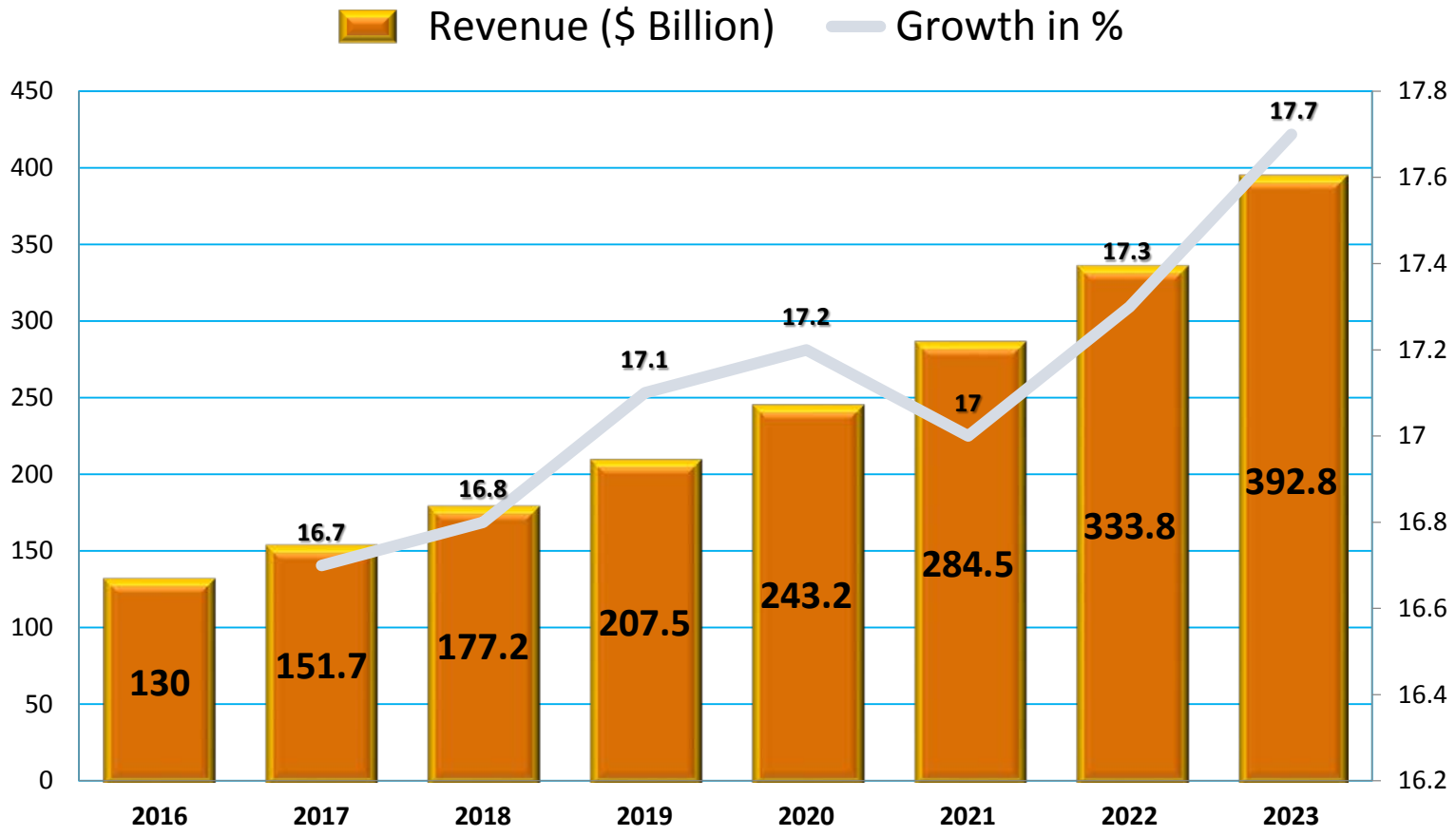
Predicting Global Nanotechnology Market Development related to Health



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Source: Infoholic Research

NCI Alliance for Nanotechnology in Cancer

Nanodelivery Systems and Devices Branch

Piotr Grodzinski, PhD
Branch Chief

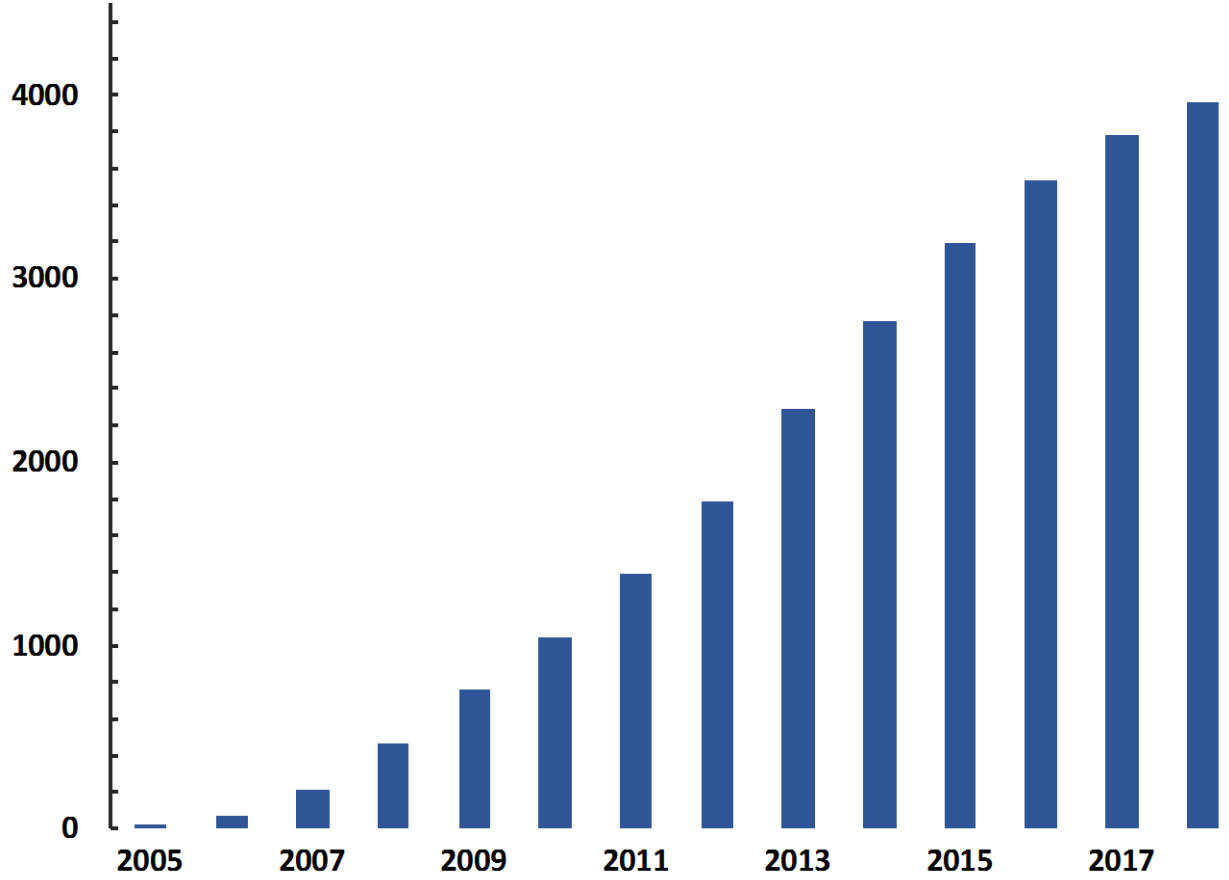
Chris Hartshorn, PhD
Program Director

Christina Liu, PhD, PE
Program Director

Luisa Russell, PhD
Program Director

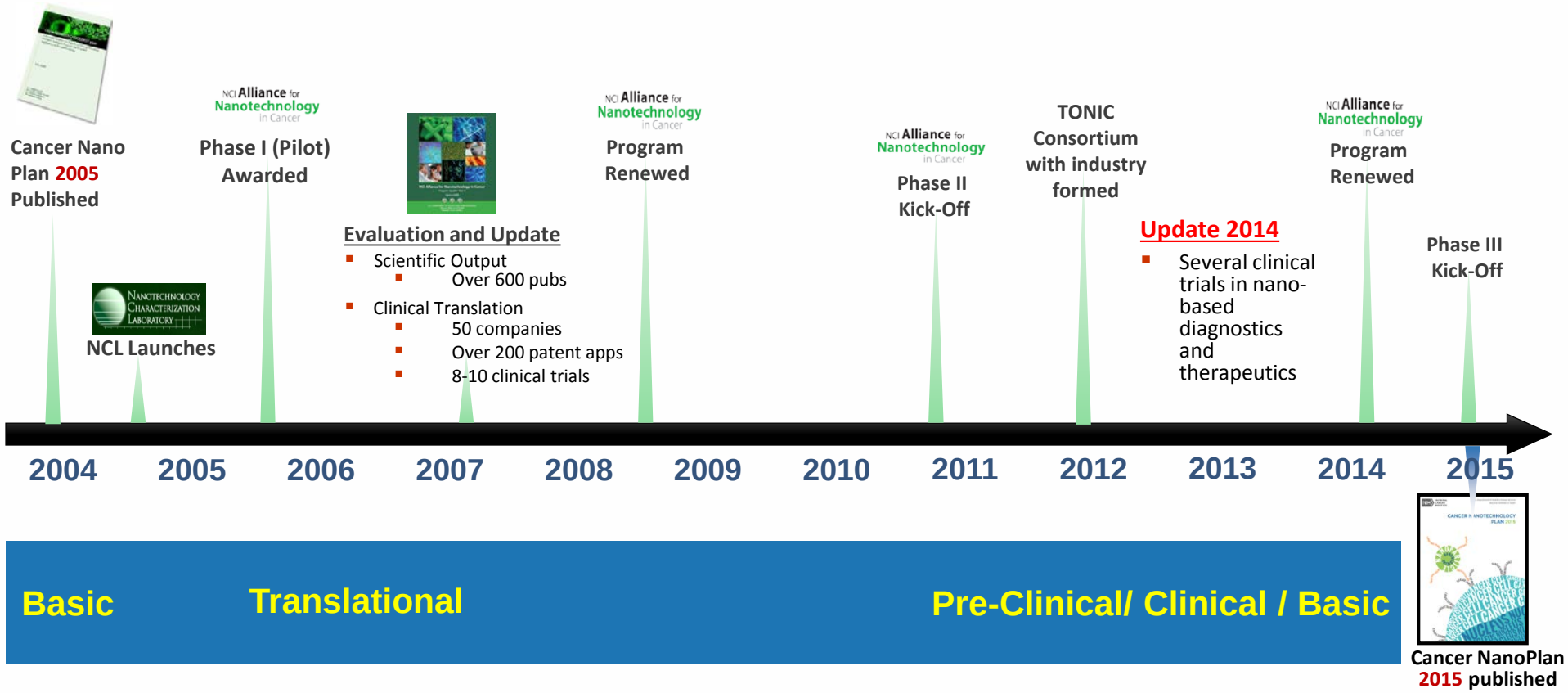
http://www.cancer.gov/sites/nano

Alliance published scientific output



NCI Alliance Timeline

NCI embraces *US National Nanotechnology Initiative* (NNI) 2001



May 2019: Will not be Renewed!

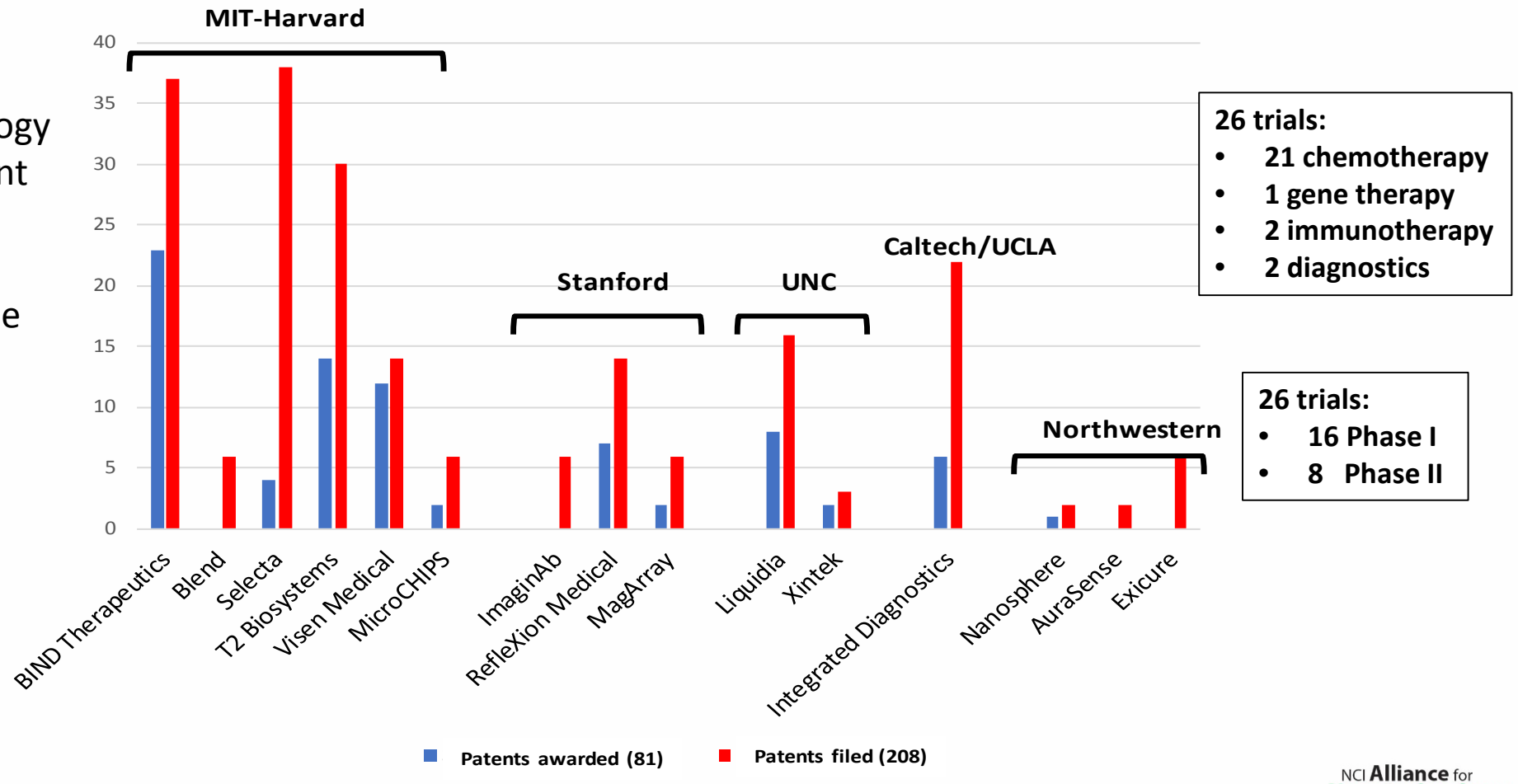
Close to **$400M *for all Alliance elements*** approved for 3 phases of the program by the NCI Executive Committee

Going Beyond NCI Funding (clinical trials and leveraged funds)

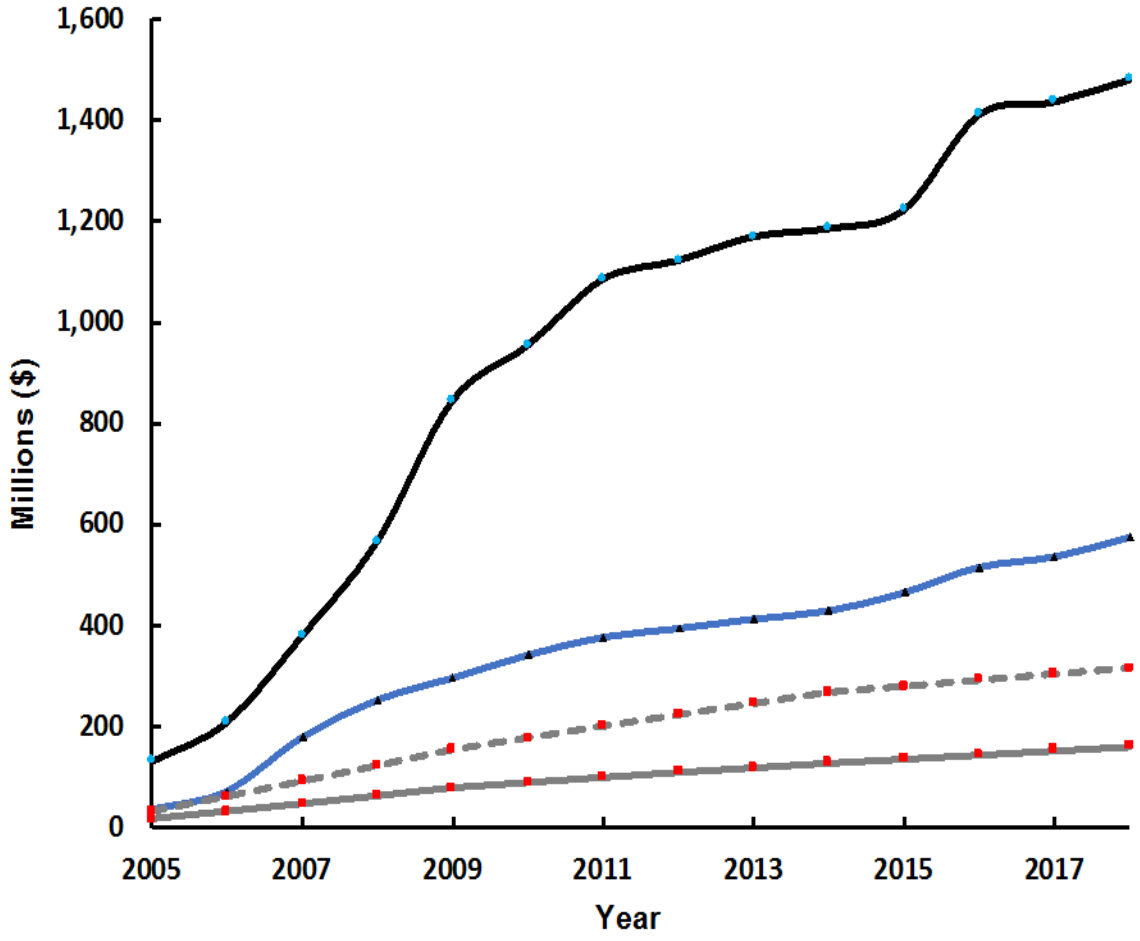
Patents awarded and filed by selected companies associated with ANC program (based on USPTO search)

Cancer Centers for Nanotechnology Excellence represent a “significant presence” that provides added value as an ecosystem:

- Illustrates development of one major field in nanomedicine
- Multidisciplinary research
- Interdisciplinary workforce
- Draws in pharma
- Multiple ROI (10x)



CCNEs – *Cumulative Public Investment vs Commercial Impact*



Leveraged Funding and Equity Raised - 4 CCNEs → **~$1.5 B**

Leveraged Funding - 4 CCNEs → **~$575 M**

Total NCI Investment - All CCNEs → **~$315 M**

Total NCI Investment - 4 CCNEs → **~$160 M**

NCI Alliance Commercialized IP

Therapeutics

- 480 Biomedical
- Adimab, Inc.
- Aduro BioTech
- Alnylam Pharmaceuticals
- Alpine Biosciences
- AM Biotechnologies
- Anterios
- Applied Proteomics
- Arrogene
- Arrowhead Pharma
- Arsenal Vascular (medical)
- Avidimer
- B3 Biosciences/B3Bio
- BIND Biosciences
- Bio-Path Holdings
- Blend Therapeutics
- Calando Pharmaceutcals
- Celldex Therapeutics
- Cellular Bioengineering Inc.
- Cerulean Pharma
- Combinent Biomedical Systems
- Consegna
- Coordination Therapeutics
- CytomX Therapeutics
- Eludica Oncology Inc.
- Exicure
- Immune Design Corporation
- Indi Molecular
- InVivo Therapeutics
- Kala Pharmaceuticals
- Kereos
- Kite Pharma (KITE)
- Kylin Therapeutics
- Leonardo Biosystems
- Lipella Pharmaceuticals
- LipoGen
- Liquidia Technologies
- Memgen
- MitoVec Inc.
- ModeRNA Therapeutics
- Molecular Therapeutics, Inc.
- Momenta Pharmaceuticals
- NanoMed Pharmaceuticals, Inc.
- NanoMedical Systems
- Nanoparticle Biochem, Inc.
- Nanospectra Biosciences, Inc.
- NanoVici
- Nemucore Medical Innovations
- Nvigen
- PACT Therapeutics
- PDS Biotechnology Corp.
- Pervasis Therapeutics
- Pharocore
- PreDx
- Pulmatrix
- Qualiber, Inc.
- Rgene Therapeutics
- RiMO Therapeutics
- Selecta Biosciences
- SemprusBioSciences
- SignPath Pharmaceuticals
- SoluBest
- TARIS BioMedical
- Valence Therapeutics

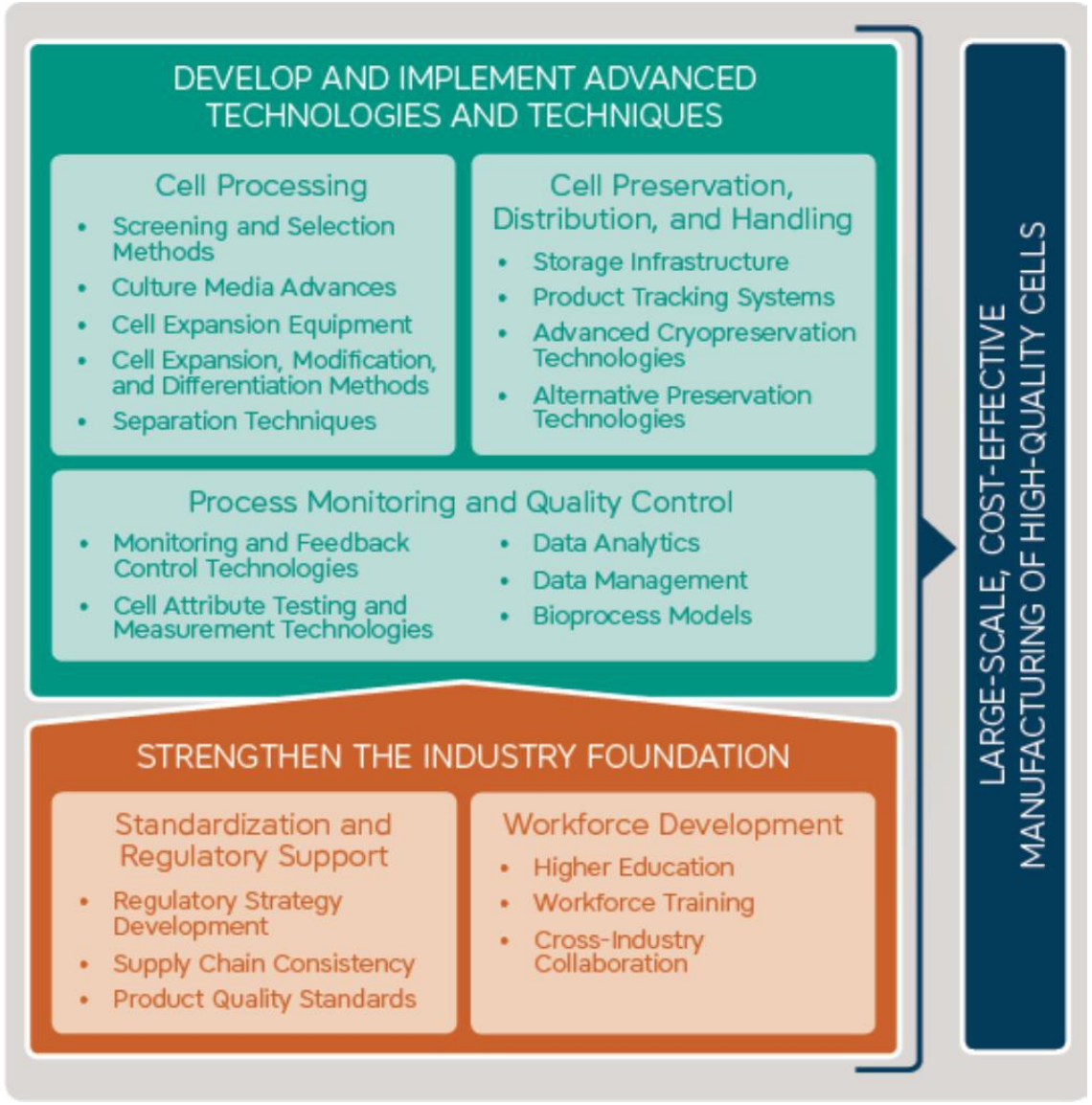
NCI Alliance Commercialized IP

Diagnostics and more

- Affinity Biosensors
- American BioOptics
- AptaMed
- Arrowhead Research Corporation
- Calhoun Vision
- Cancer Targeting Systems
- Carbon
- Carestream Molecular Imaging/Health
- CellSight Technologies
- DiagNano
- Eludica Oncology Inc.
- ENDRA Life Sciences
- Enlight Biosciences
- Gensign
- Grzybowski Scientific Inventions/Chematica
- ImaginAb
- Imbio
- Indi Molecular
- Indi
- Isoplexis
- Living Proof
- Lumera Corp
- Lumicell Diagnostics
- MagArray
- Materia
- MDxHealth
- MicroCHIPS Biotech
- Micromod
- Molecular Biomarkers (MoB)
- Molecular Imaging Research
- Nanogen, Inc.
- NanoInk
- Nanoplex Technologies
- NanoSonix
- Nanosphere
- Nine Point Medical
- Nodality
- Ocean Nanotech, LLC
- Ohmx
- Oncovance Technologies Inc
- Optical Micro-Machines
- Oxonica
- Parallel Solutions, Inc
- PixelEXX Systems
- Principio
- ProChimia Surfaces
- Regis Technologies
- SAMDITech
- Seventh Sense Biosystems
- Sophie Biosciences
- T2 Biosystems
- Tactic Pharma
- VisEn Medical
- Visual Sonics
- Vivonetics
- XinRay Systems
- Ziva Corporation
- Zymera

Other Agencies: NSF Engineering Research Centers

e.g., ERC for Cell Manufacturing Technologies



Impact on Industry and Economy

"... cell therapy is the fastest growing segment of regenerative medicine and also the largest. Globally, the stem cell therapy market is expected to be worth U.S. $40 billion by 2020 and U.S. $180 billion by 2030"

Healthcare & Life Sciences, Frost & Sullivan, PR Newswire, July 28, 2015

T cell therapy market will be worth U.S. $30 billion by 2030.

Research and Markets, October 2015

Goals: Establish Industry-Clinician-Academia-Government Partnership

- **Identify Barriers and Challenges**
- Develop an **Industry-driven, 10 year Roadmap** to address barriers and challenges
- **16 Universities and Clinical GMP Centers,**
- **27 Industry partners**
- **FDA, DOD, NIH, NSF, and NIST**

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European Institutions and Platforms in Nanomedicine

European Technology Platform for Nanomedicine (ETPN)

- **1700 Institutions in Europe**
- **15 Plattforms**
- **European Technology Platform for Nanomedicine (ETPN)**
- **ESNAM (European Society for Nanomedicine Part of the international Society of Nanomedicine (Europe, USA, Canada, Republic of Korea, South Africa, India, China, Japan, Australia)**
- **European Characterization Center (EUNCL) for ETPN**
- **European Foundation for Clinical Nanomedicine (CLINAM) Research, Dissemination, Global Networking**
- **CLINAM annual summit with 500 people from 40 countries - the world's largest clinical Nanomedicine summit**

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Source: ETPN

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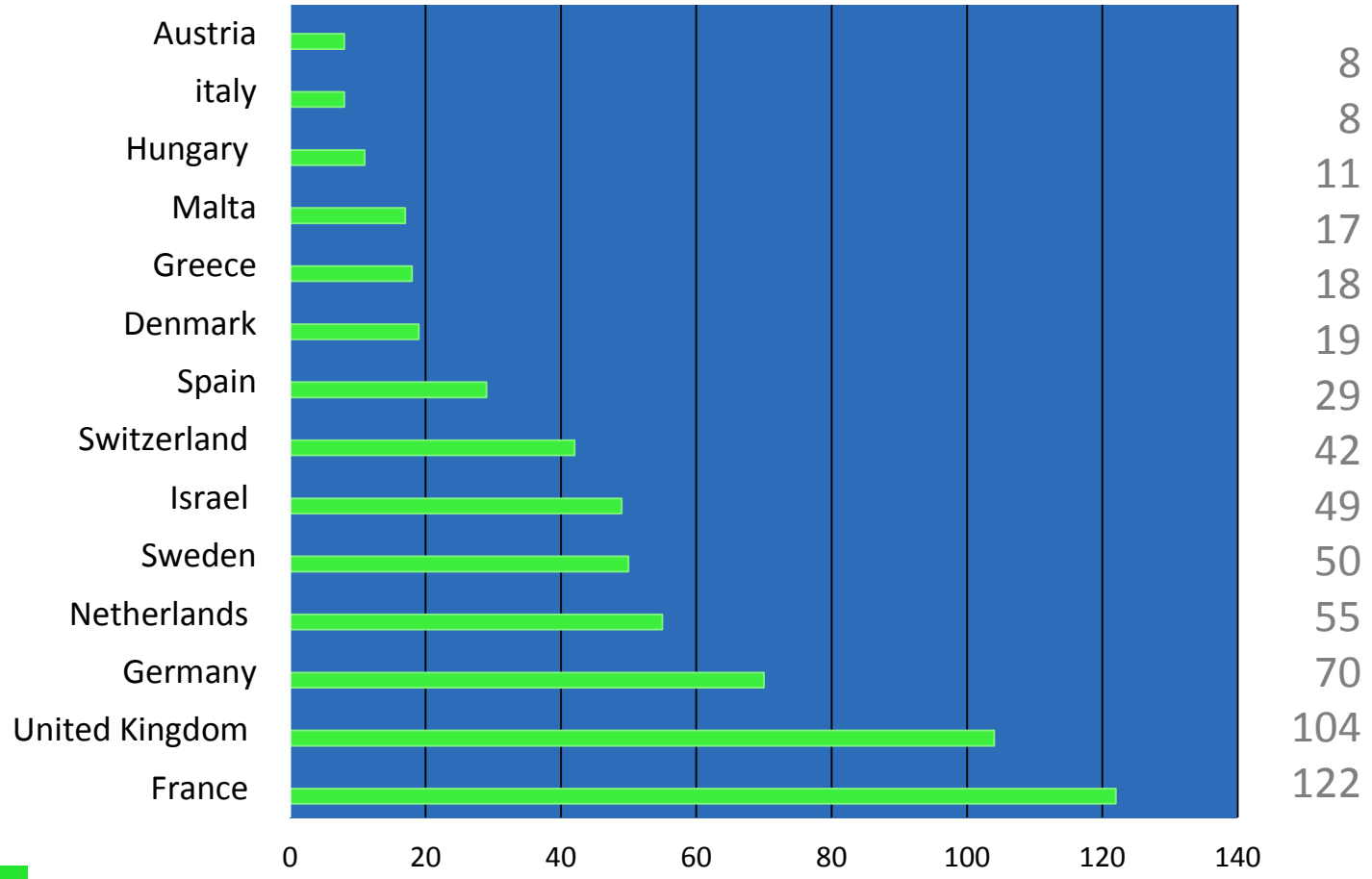
620 Nano-Drug Projects in the European Pipeline

in Research, Preclinical, Phase 1,2,3, Approved and Marketed



12 other countries share
~ 20 PROJECTS

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Gap between USA and China in Nanotechnology has Narrowed Significantly: American Nanotechnology Leadership faces Significant Challenges

"Small Science in Big China"

FIGURE 1 | GROWTH OF NANOSCIENCE.
The total output of papers related to nanoscience and technology published in journals listed in the SCI has been growing for the past two decades.

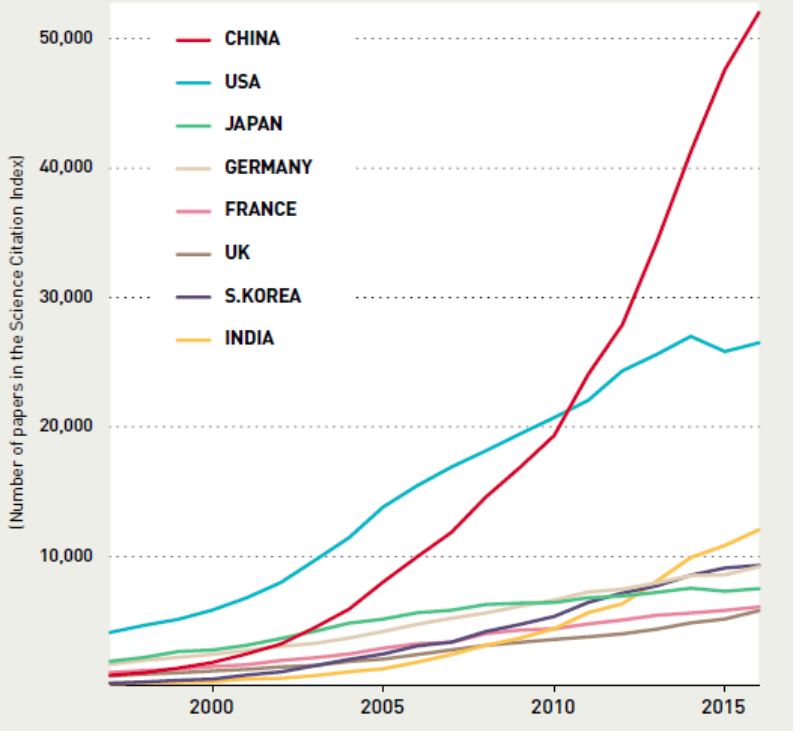
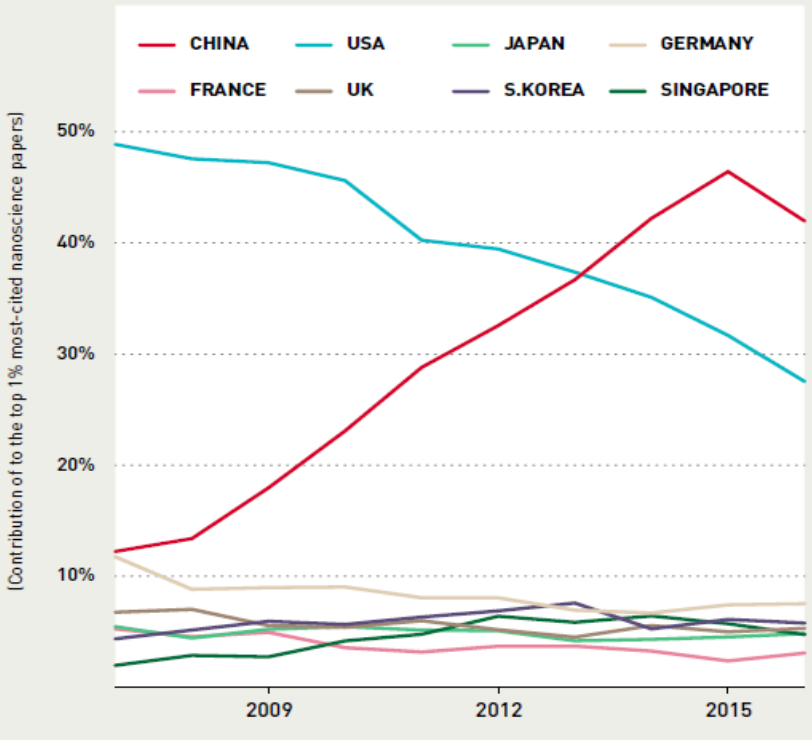


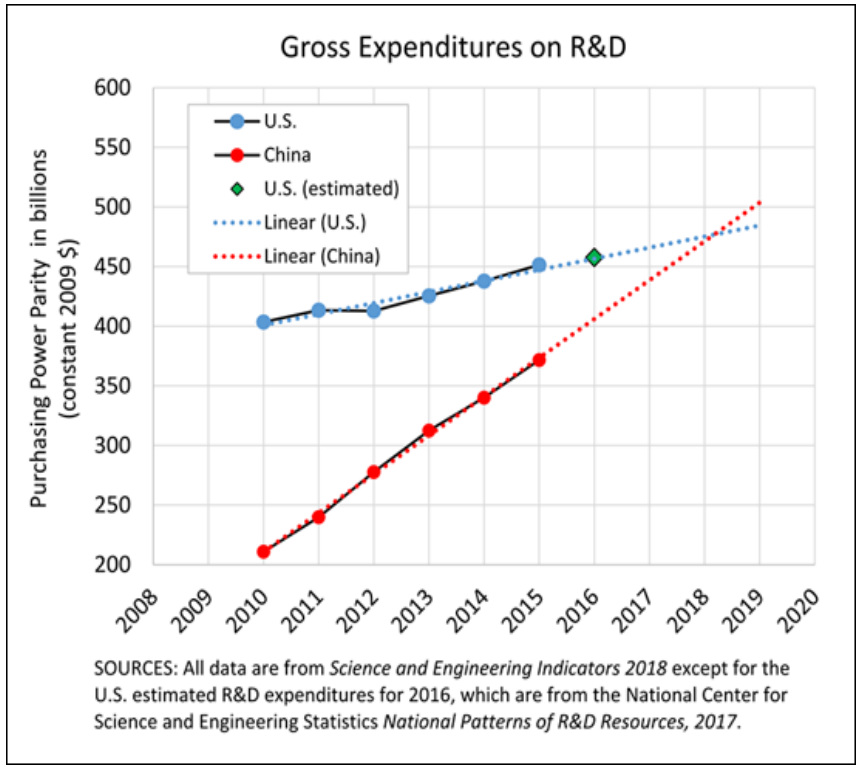
FIGURE 4 | GROWTH OF HIGH-IMPACT NANOSCIENCE.
China is now the largest contributor to the top 1% most-cited papers related to nanoscience and technology.



https://media.springernature.com/full/springer-cms/rest/v1/content/15302926/data/v3

International Nanotechnology-related patent applications:
China has overtaken the US (multiple fold)

Purchasing Power Parity



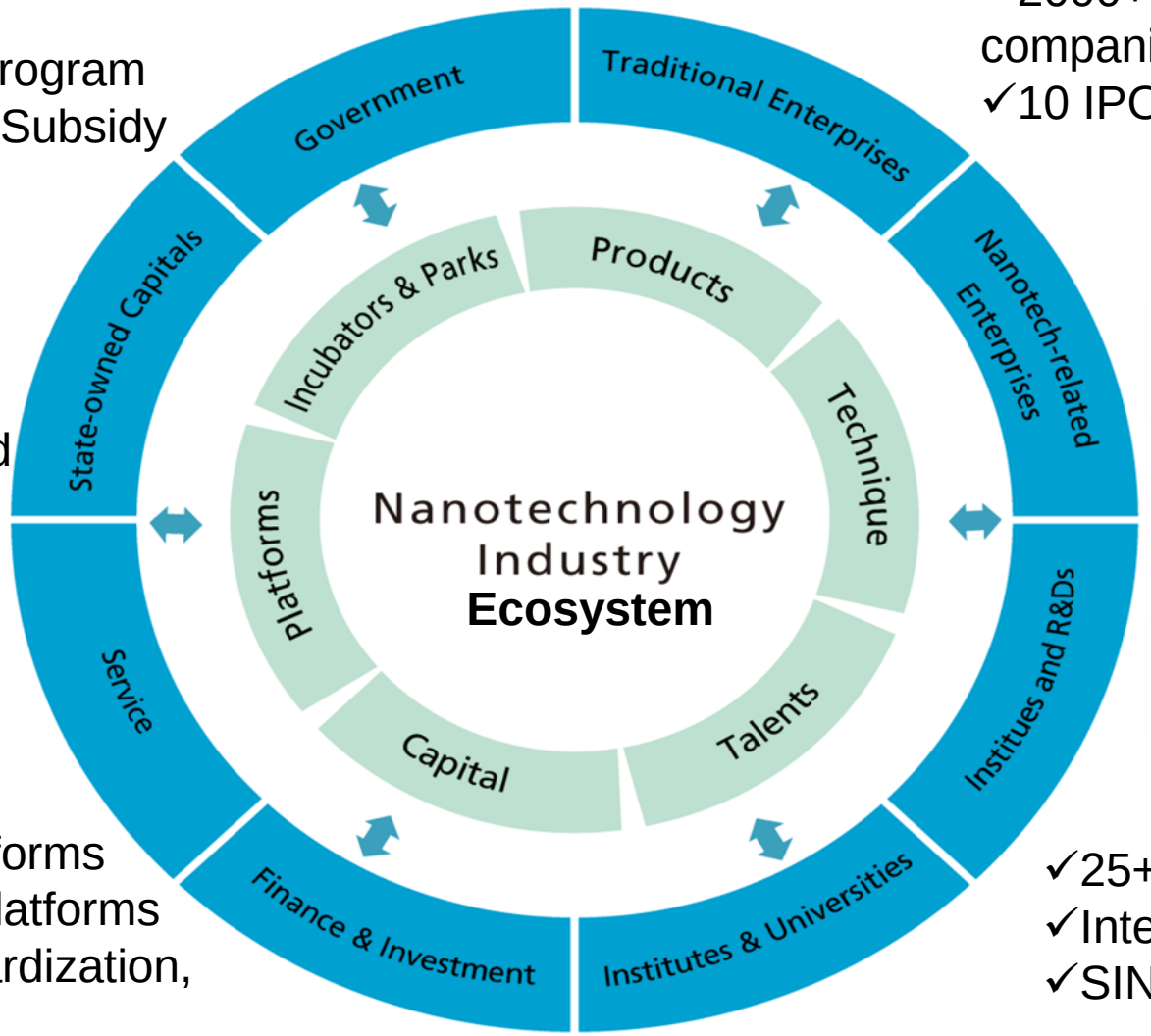
Chinese R&D increased by 18% annually 2000-2015 (US 4%).
R&D rise for nano and biotech even steeper

https://eos.org/articles/china-may-soon-surpass-the-united-states-in-rd-funding

CHINA

✓Tax Incentives
✓Tech-Pioneer Program
✓Grant & Rental Subsidy
✓Talent Support

✓4000+ WFOEs
✓2000+ High tech companies
✓10 IPOs



230+ Startups & Enterprises

✓20+ VCs
✓80+ PEs
✓Nano VC

✓Incubators
✓Building & Land
✓Application
✓Match Making
✓Promotion

✓**Composite material**
✓**Li-on Battery**
✓**GaN**
✓**Nano Carbon**
✓**MEMS**
✓**Diagnostics**
✓**Quantum science**

✓Technical Platforms
✓Engineering Platforms
✓Safety, Standardization, IP Protection

✓25+ Univ. and graduate Schools
✓International Cooperation
✓SINANO

Policy: Identify specific areas as Centers of Excellence and then building up an ecosystem in each location, frequently around a university, CAS institute

ATIP Briefing to PCAST Apr. 2014
Dr. David K. Kahaner
kahaner@atip.or.jp

The Suzhou Industrial Park Unlike Anything Else in the World!

Represents China's shift from manufacturing to the inclusion of R&D with a particular focus on nanotech commercialization

Suzhou Institute of Nanotech

Suzhou recognizes nanotech as key enabler for transforming Chinese industry. In collaboration with CAS, it built the first application driven research institute to serve as hub of innovation

Suzhou Biobay

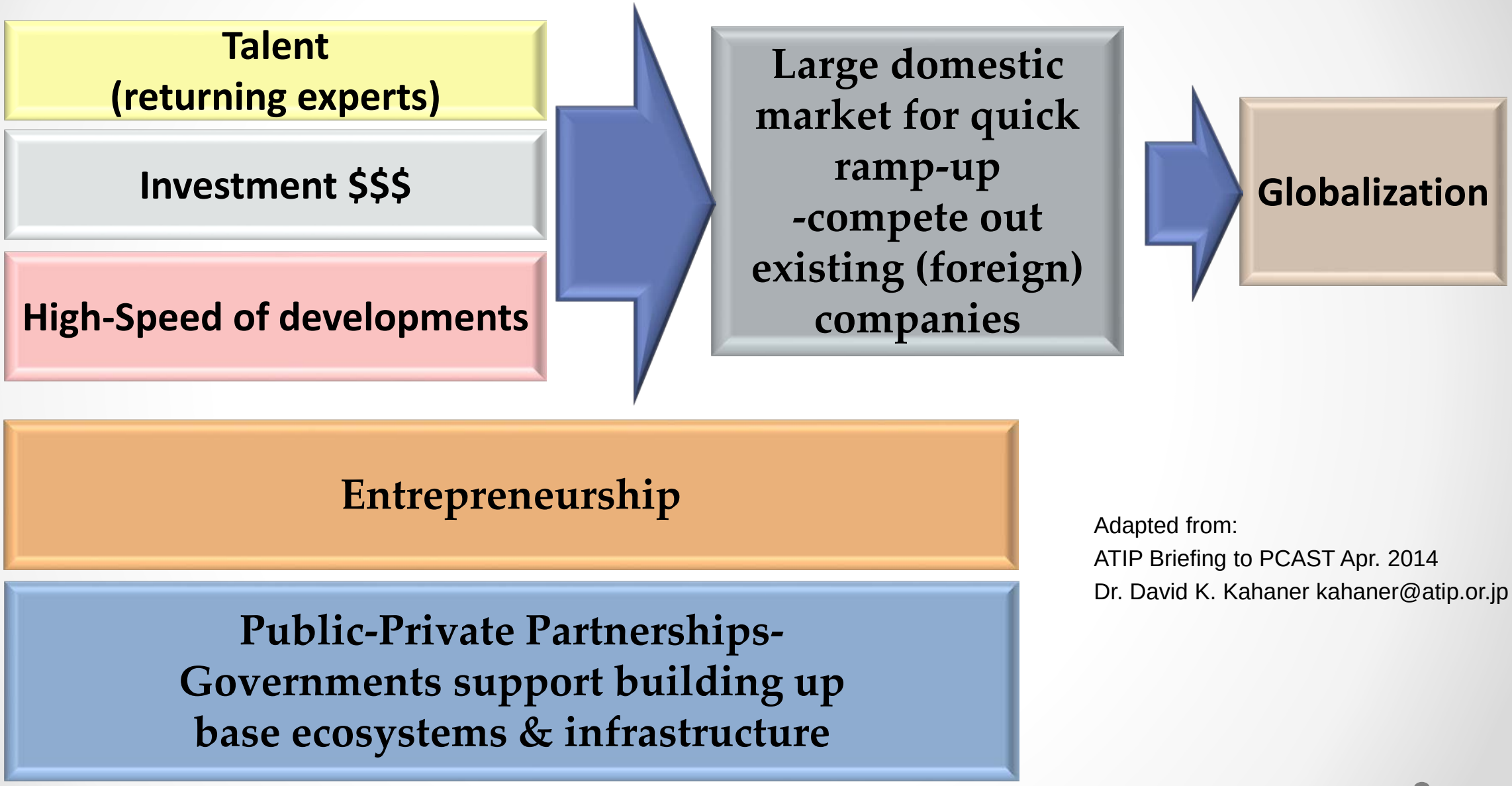
Suzhou Biobay is the most progressive bio-nano incubator in China. Biobay assists bio&nano enterprises to raise funds through the Suzhou Industry Park (SIP) awards, government funds and venture capitals

Nanopolis Suzhou

Nanopolis, an area of 1 sq km, is equipped with integrated services for R&D, technology incubation, pilot & mass production, corporate HQ, conference & exhibition facilities and other auxiliaries.

CHINA

The Dynamics Driving It



Adapted from:
ATIP Briefing to PCAST Apr. 2014
Dr. David K. Kahaner kahaner@atip.or.jp

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Future Nanomedicine Ranking of Continents 2022/23

Personal opinion: Dr. med. h.c. Beat Löffler MA, CEO

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Asia-Pacific region (incl. China, Japan & India) — 1

- Fastest growing market in the world
- Highest unmet needs in healthcare
- Cheaper workforce attracts Overseas Companies and Investment

USA (incl. Latin America) — 2

- Most Nanomedicine start-ups worldwide
- Private philanthropic funding
- World's largest influence in regulatory matters (FDA NIC)
- Risk Taking Mentality of entrepreneurs

Europe — 3

- Industry leaves to where workforce is cheaper
- EU strategy is hampered by bureaucracy and multicultural composition

Australia / New Zealand — 4

Slowly catching up Development – will get a bigger market

Africa and Middle East (and rest of world) — 5

- Depending on the other markets and rather slow development .

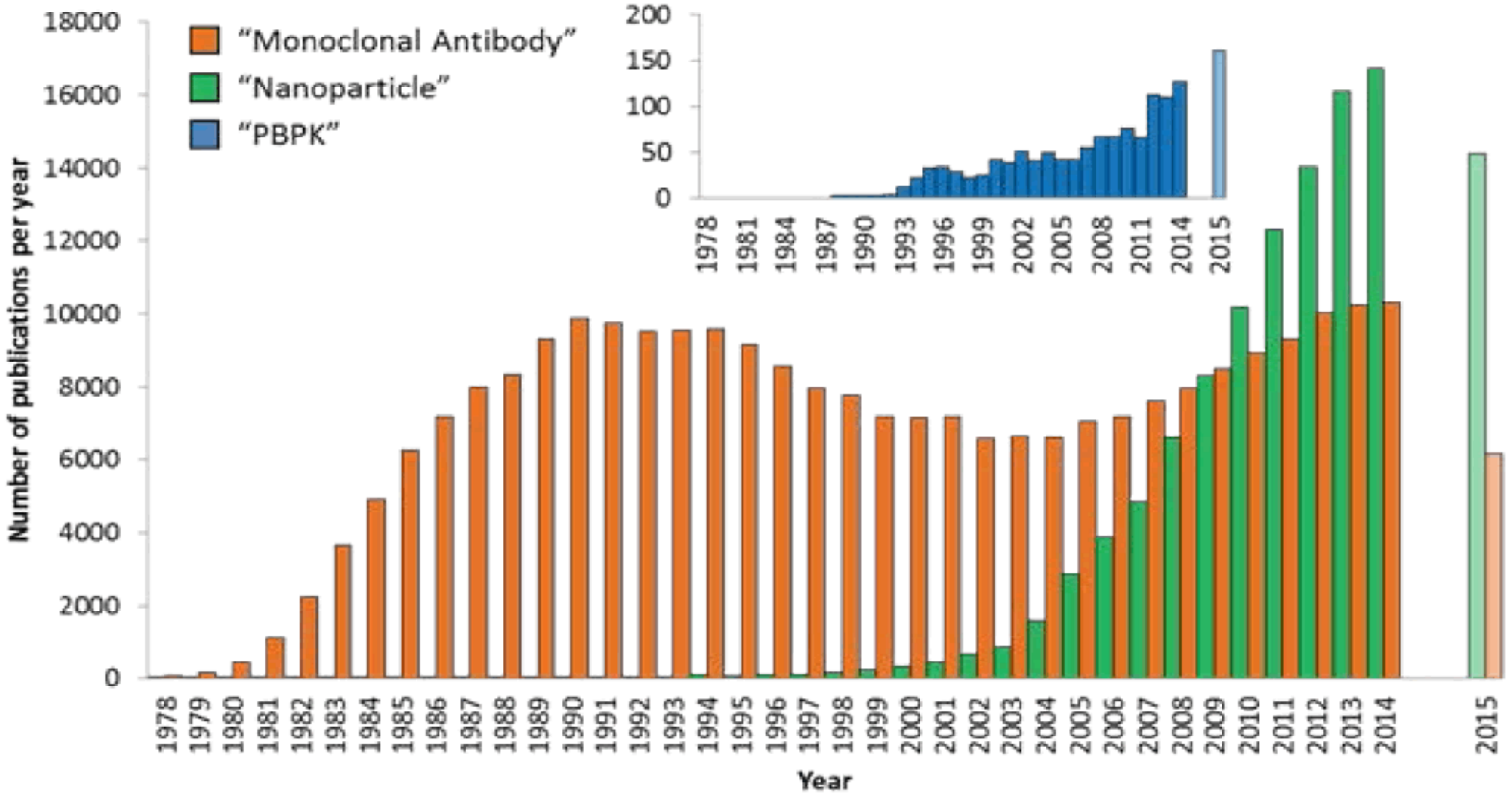
Perceptual Challenges for Nanomedicine

- Timescale to deliver on a promise
- Number of drugs approved compared to the scale of investment
- Safety of nanomaterials and nanodrugs (risk averse approach big companies)
- Confusion about what is and what is not a nano drug (reflect risk aversion?)
- Lagging nano-specific regulatory guidelines

Perceptual Challenges for Nanomedicine

- Cost-benefit considerations (takes 10-15 years and $1 billion per new drug)
- Nanodrugs have more often improved safety rather than efficacy
- Nano formulations for chemo have not changed cancer survival
- 70% of nano patents are non-reproducible
- Patent process overly broad for composition of matter claims, not appreciating the subtleties drug specific development

The Timeline to Deliver on a Promise: Investing in Entire Field, not just a Technology



Journal of In Silico & In Vitro Pharmacology

- It took ~20 years for monoclonal antibody therapies to move from the lab to the clinic – majority of FDA approvals occurred after year 2000
- Nanomedicine represents a series of different fields, each with its own science development requirements and assembly of interdisciplinary teams to shape the workforce and deliverables

Safety Issues

- Lack of standard protocols or uniformity of testing by different stakeholders
- Physicochemical characterization has not been standardized
- Poor prediction making of *in vitro vs in vivo* outcomes
- New structure-activity relationships continue to emerge & require adaptation to disease process
- Complex interplay between controlled, engineered material properties *vs.* dynamic, heterogeneous, and changing biological environment
- Precise control of biodistribution, access to the disease site and drug release still emcumber uncertainties
- FDA guidelines are not nano-specific: what will happen for therapeutics relying on intrinsic nanomaterial properties or non-degradable nanoparticles?

Roche's Position on Nanotechnology
(reviewed March 2019)

"…Nanotechnology includes the ability to create and to manipulate materials… … may attain novel characteristics that have led to nanotechnology being viewed as one of the key technologies of the 21st century

Nanotechnology is still a new and evolving field for scientists to explore, and as such, many unanswered questions remain

Roche takes a favorable position towards active, safety-aware research in the field and opposes any actions that would ……. block the development of potential benefits from nanotechnology

The risks and benefits of nanotechnology have to be carefully evaluated, especially if it is to be implemented in applied medicines or therapies.

While applications of nanotechnology are expected in multiple areas, Roche's interest in nanotechnology is presently focused on:

- Starting materials to manufacture labels for in-vitro diagnostics
- Materials and surface coatings for pharmaceutical products, sensors and test strips
- As of now final products do not contain nanoparticles "

Source: www.roche.com/dam/jcr:648a48b8-9d78-4d81-bd12-32ec1f96141a/en/13_Position_Nanotechnology_reviewed_4_2017.pdf

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Nanomedicine Products – What is one and what is not?

Depending on DEFINITION: 140 - 158 realized drugs, many of them not declared as nanomedicines

Milled organic Nanocrystalline drug

Brand	Manufacturer	2014	2015	2016	CAGR
Abraxane	**Celgene**	848.2	967.5	943.1	5.5%
Alimta	**Eli Lilly**	2,291.0	2,493.1	2,322.3	0.7%
Eligard	**Astellas Pharma**	-	2,660.0	2,464.0	43.6%
Copaxone	**Teva Pharmaceutical**	4,237.0	4,023.0	4,100.0	7.4%
Rapamune	**Pfizer**	339.0	197.0	174.7	28.2%
Neulasta	**Amgen**	4,392.0	4,715.0	4,500.0	1.2%
Cimzia	**UCB SA**	836.9	1,100.0	1,264.2	22.9%
AmBisome	**Astellas Pharma**	388.0	350.0	349.3	5.1%
Mircera	**Hoffmann-La Roche**	404.5	460.8	485.0	9.5%
Pegasys	**Hoffmann-La Roche**	984.6	521.9	277.4	46.9%
Emend	**Merck & Company**	553.0	535.0	540.0	1.2%
Renagel	**Sanofi**	718.2	972.4	928.2	13.7%
Ritalin	**Novartis**	492.0	365.0	278.7	14.7%

Dr. med. h.c. Beat Löffler MA, CEO
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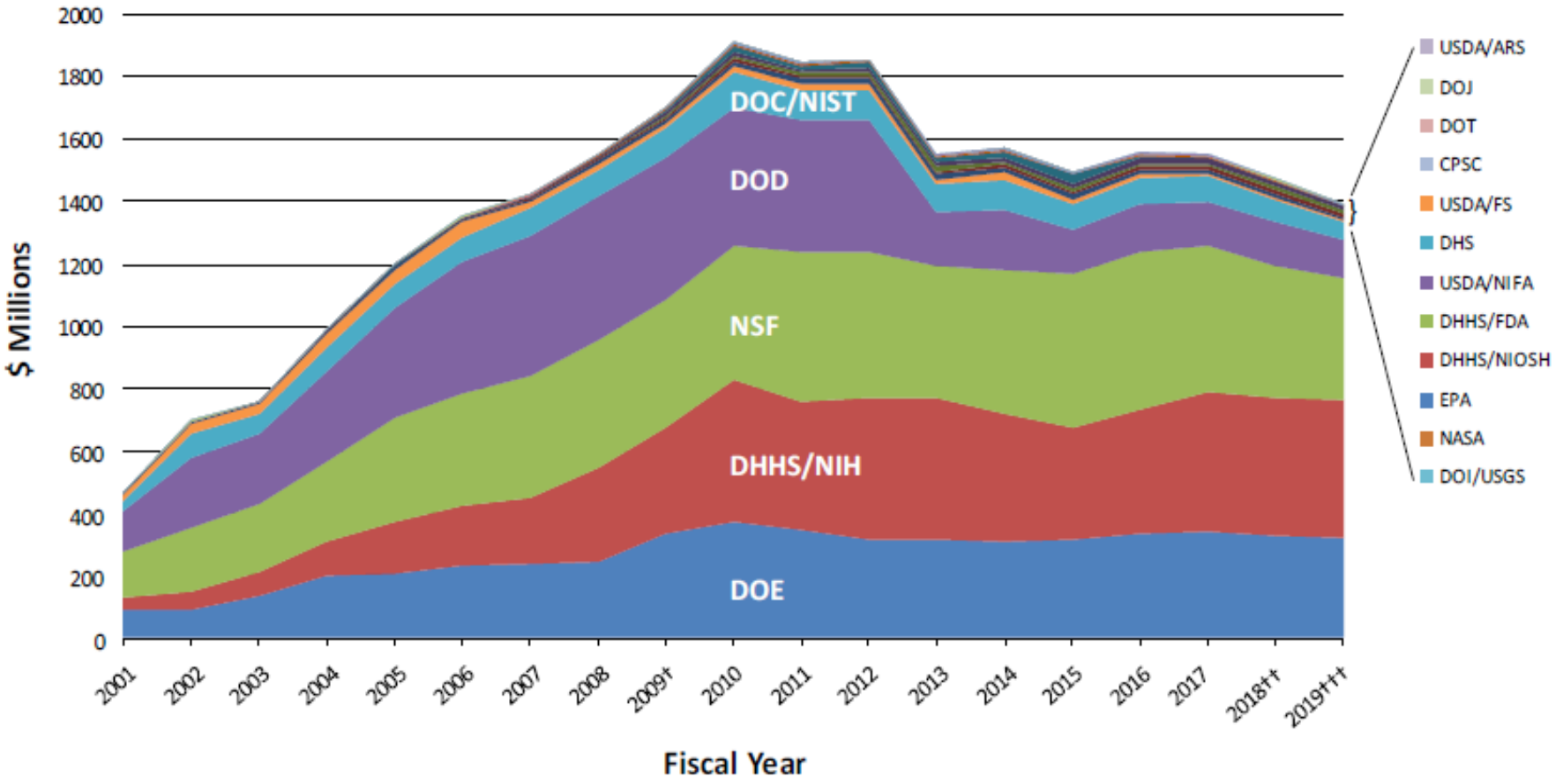
Source: Infoholic Research

NNI Funding by Agency, 2001–2019.



The NNI does not have centralized funding. Funding is provided directly through collaborative efforts by NNI member agencies. NNI has invested approximately $24 billion in nanotechnology R&D since 2001

Opinion: NNI Should Continue to Advance US Global Competitiveness

Why (from a healthcare perspective)?

- US Commitment to Compete: Nation-at-Risk Report (1983, Education), America Competes Act (2007, STEM), Rising above the Gathering Storm (2007, Marketplace and Economics) *vs.* Commitment to *Compete Until the Promise is Realized and we have Risen Above the Storm*
- Several healthcare areas in critical need of game-changing solutions coming from nano:
  - Personalized medicine (gene/nucleic acid delivery, non-invasive quantum imaging)
  - Ageing (e.g., stealth NP bypassing the blood brain barrier for Alzheimer's)
  - Regenerative medicine (3D printing of bio mimicking materials)
  - Nanoparticle vaccines/tolerogenic nanoparticles
  - Cancer treatment, including immunotherapy
- Entrepreneurship cannot substitute for the multidisciplinary workforce that is required
- Healthcare cost increase as a result of having to import innovative technology
- Brain drain to where innovation is funded and aggressively commercialized
- Convergence of nano-enabled therapeutics with artificial intelligence, etc

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Nanomedicine in the mix of Personalized Medicine

Personalised Medicine

Biotechnology	Nanotechnology	Genetics
Discovery of a Drug (Screening)	Discovery particle	Discovery of single or muliple fuctions
Drug Delivery	Translation Process	Symptomatic analysis/Test
Therapy	Safety Aspects/ Trials/Approving	Tools adaption
Product	Product	Therapy

Adapted from: Dr. med. h.c. Beat Löffler MA, CEO

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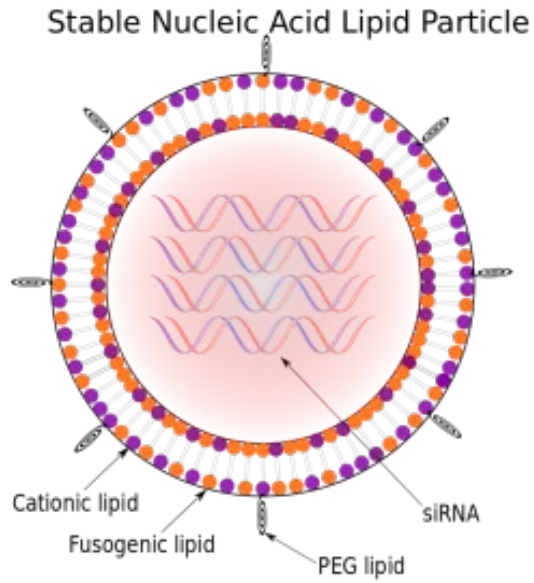


Onpattro (patisiran) for Heriditary Amyloidosis (FDA approved 2018)

https://biopharmconsortium.com/2018/09/05/alnylams-patisira

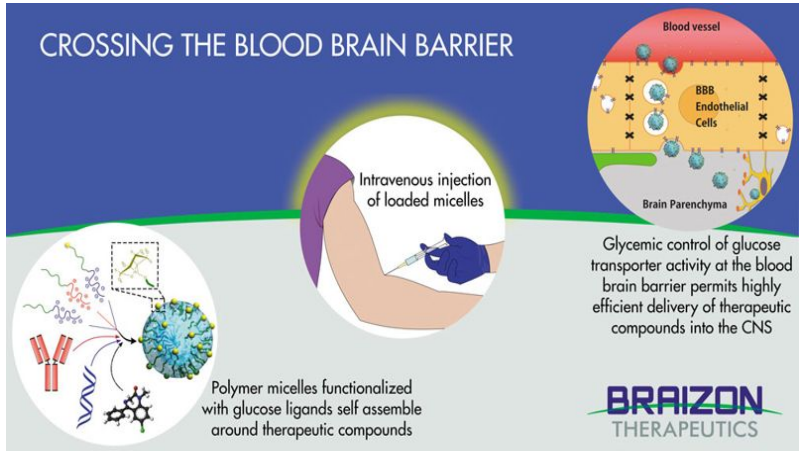
Nanomedicine Recommendation

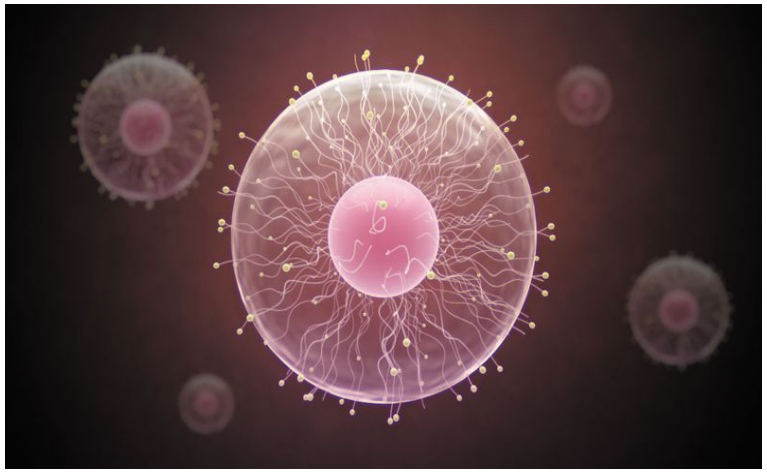
- Continue to invest in Multidisciplinary Ecosystems & Training, including Nano Cancer
- Signature Initiative for Nanomedicine
- Nanomedicine Grand Challenges

Nanomedicine in Japan

adapted from: Nature https://www.nature.com/collections/zmpvwjpfpd

Groundbraking Grand Challenges that address: Old age, Cancer, Neuroscience. “Japan has pumped millions into pursuing the dream of invisible devices, working from within to detect, diagnose and treat. It’s a strategy on the cusp of reaping significant rewards”





“Quantum imaging making personalized medicine a reality: Nanoparticle-amplified MRI concept used to select the size and property of nano-platforms that can be delivered, and to predict their therapeutic efficacy”.

“Stealthy nanomachines bypass brain's defences: Braizon Therapeutics Inc has found a cunning way to get pharmaceuticals past the blood-brain barrier by using nanotechnology to piggyback aboard glucose transporters”.

“A Nano-hospital in every body: The ambition is grand and the timeline spans decades: the development of nanomachines dispersed in the human body, performing detection, diagnosis and treatment and communicating wirelessly with physicians who monitor and direct treatment”