Hot Topic Discussion

A Fresh Look at the Commercial Activity of Cancer Nanomedicines

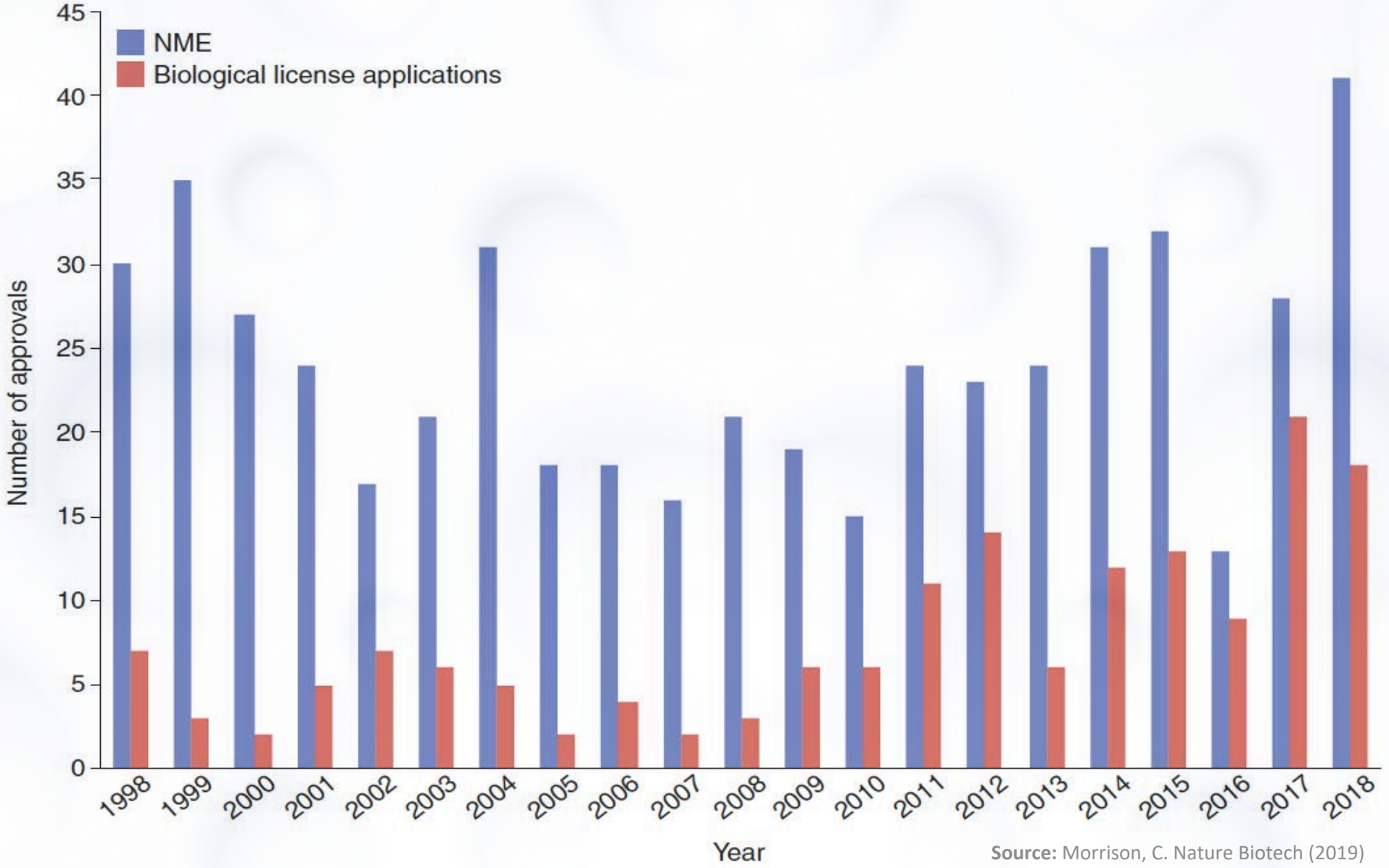
Arnav Chhabra (Bhatia Lab)

February 25, 2019

MARBLE CENTER FOR CANCER NANOMEDICINE
Small technologies, BIG impact

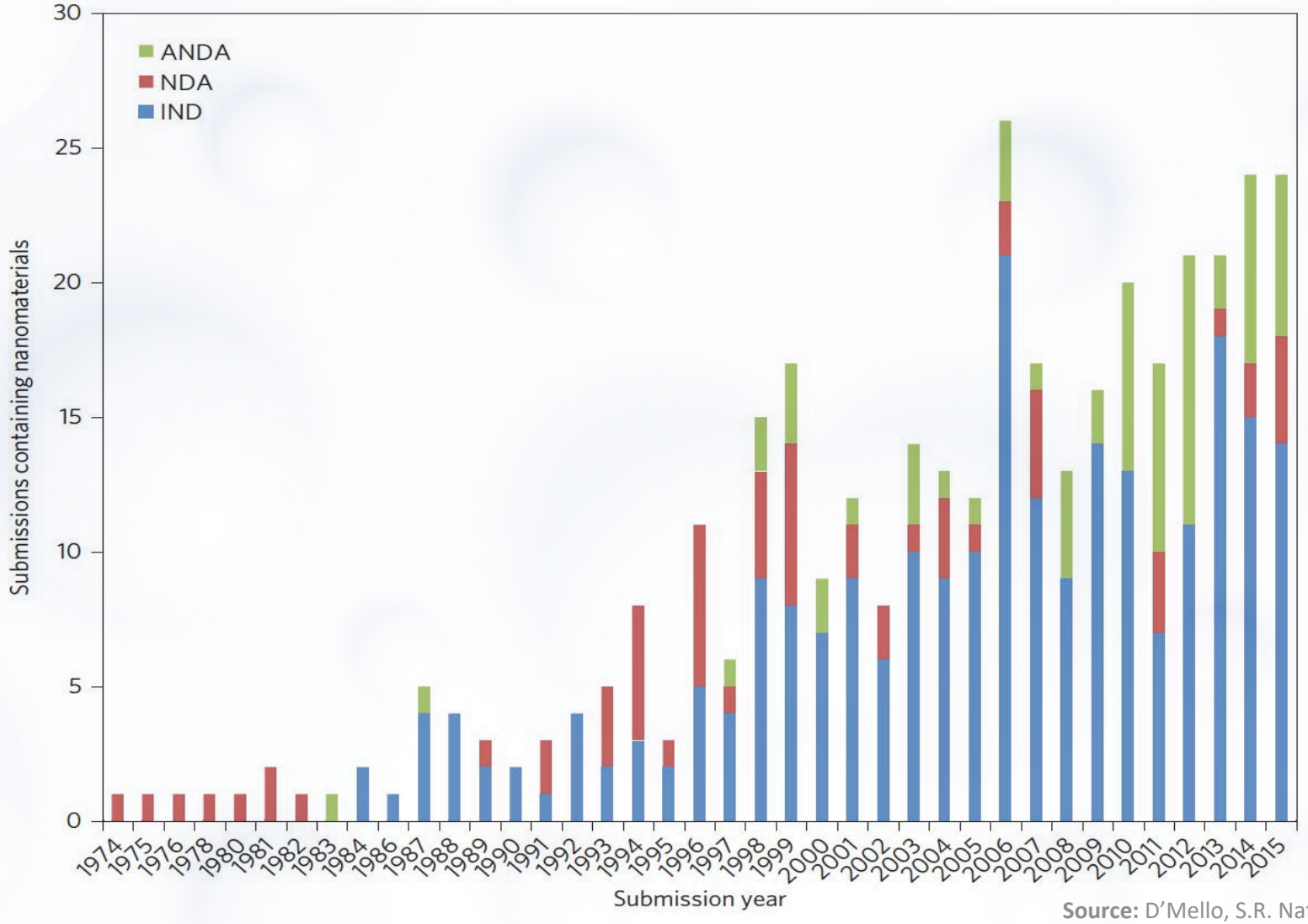
KOCH INSTITUTE
for Integrative Cancer Research at MIT

FDA's Record-Setting Year for Approvals

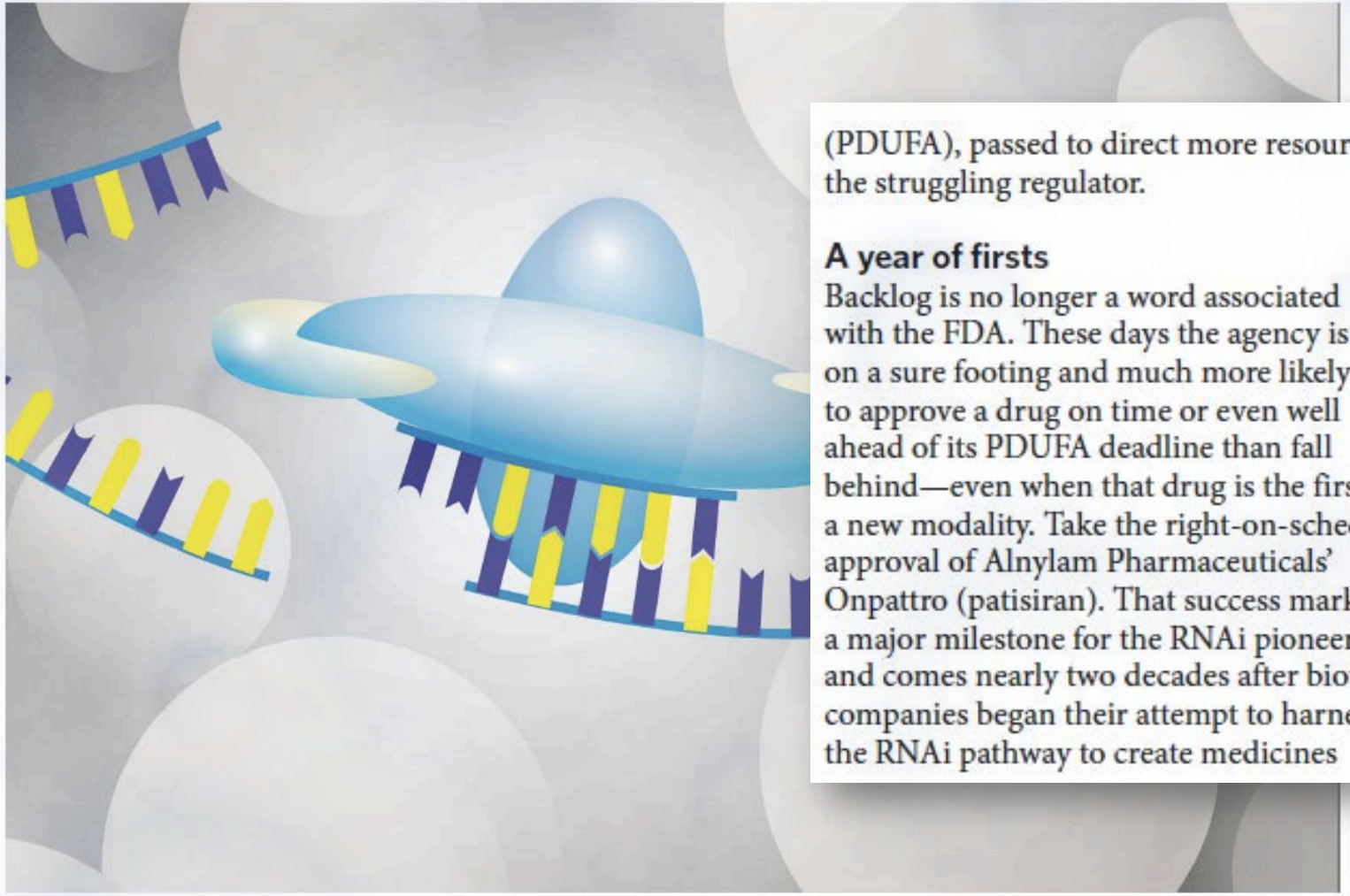


Source: Morrison, C. Nature Biotech (2019)

Increase in Nanomaterial Product Applications Submitted to FDA



Source: D'Mello, S.R. Nature Nanotechnology (2017)



(PDUFA), passed to direct more resources to the struggling regulator.

A year of firsts

Backlog is no longer a word associated with the FDA. These days the agency is on a sure footing and much more likely to approve a drug on time or even well ahead of its PDUFA deadline than fall behind—even when that drug is the first of a new modality. Take the right-on-schedule approval of Alnylam Pharmaceuticals' Onpattro (patisiran). That success marks a major milestone for the RNAi pioneer and comes nearly two decades after biotech companies began their attempt to harness the RNAi pathway to create medicines (*Nat. Biotechnol.* **36**, 775, 2018). Onpattro, a small interfering RNA (siRNA) 21-mer oligonucleotide containing 2′-O-methyl modified and unmodified ribonucleosides, with 2′-deoxy-2′-fluoro-modified thymidine dinucleotide overhangs at the 3′ ends, encapsulated in a cationic amino MC3 lipid nanoparticle, received the FDA nod in August to treat hereditary transthyretin-mediated amyloidosis (hATTR), a rare and sometimes fatal disease that causes damage to organs and peripheral nerves from the buildup of amyloid. Alnylam's new drug application was extensively decorated with regulatory incentives, as is increasingly common. The first-in-class Onpattro received FDA's Breakthrough

Fresh from the biotech pipeline—2018

The FDA approved record numbers of new molecular entities, orphan drugs, small-molecule generics and biosimilars in 2018. Could industry's regulatory success of the past two years become the new normal?

Source: Morrison, C. Nature Biotech (2019)

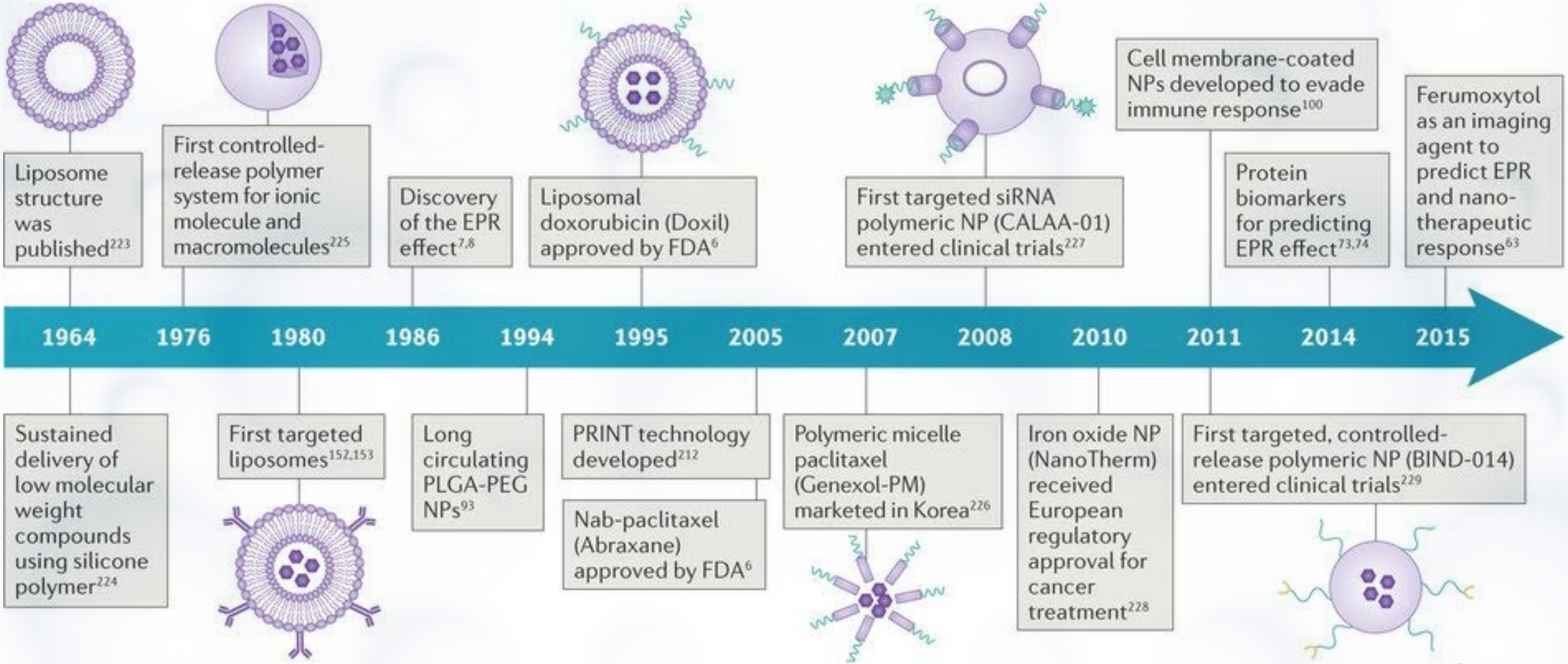
Top 20 Most Valuable R&D Projects (Ranked by Net Present Value)

Source: Evaluate, May 2018

Rank	Product	Company	Phase (current)	Pharmacological Class	WW Product Sales ($m) 2024		Today's NPV ($m)	
1.	**VX-659 + Tezacaftor + Ivacaftor**	Vertex Pharmaceuticals	Phase III	Cystic fibrosis transmembrane regulator (CFTR) potentiator & corrector	3,485	New Entry	**13,070**	
2.	**Upadacitinib**	AbbVie	Phase III	Janus kinase (JAK) 1 inhibitor	2,570		**9,878**	
3.	**Aducanumab**	Biogen	Phase III	Anti-beta-amyloid (Abeta) MAb	2,245		**8,414**	
4.	**Brolucizumab**	Novartis	Phase III	Anti-vascular endothelial growth factor (VEGF) antibody fragment (Fab)	1,800	New Entry	**8,123**	
5.	**GSK2857916**	GlaxoSmithKline	Phase II	Anti-B-cell maturation antigen (BCMA) antibody-drug conjugate	1,367	New Entry	**7,498**	
6.	**Lanadelumab**	Shire	Filed	Anti-plasma kallikrein MAb	1,569		**7,476**	
7.	**ARGX-113**	argenx	Phase II	Anti-neonatal Fc receptor (FcRn) MAb	1,941	New Entry	**6,496**	
8.	**Semaglutide Oral**	Novo Nordisk	Phase III	Glucagon-like peptide (GLP) 1 agonist	1,994	New Entry	**6,452**	
9.	**JCAR017**	Celgene	Phase II	Anti-CD19 chimeric antigen receptor (CAR) T cell therapy	1,154	New Entry	**6,258**	
10.	**BAF312**	Novartis	Phase III	Sphingosine-1-phosphate (S1P) 1 & 5 modulator	1,541	New Entry	**5,814**	
11.	**Elafibranor**	Brokers Forecasting an Undisclosed Licensing Partner	Phase III	Peroxisome proliferator activated receptor (PPAR) alpha & delta agonist	1,670	New Entry	**5,691**	
12.	**Risankizumab**	AbbVie	Phase III	Anti-IL-23 MAb	2,114	New Entry	**5,495**	
13.	**AVXS-101**	AveXis	Phase III	Survival motor neuron (SMN) gene therapy	1,788	New Entry	**5,453**	
14.	**Elafibranor**	GENFIT	Phase III	Peroxisome proliferator activated receptor (PPAR) alpha & delta agonist	1,200	New Entry	**5,422**	
15.	**Luspatercept**	Celgene	Phase III	Activin receptor (ACVR) type 2b antagonist	1,168	New Entry	**5,050**	
16.	**LentiGlobin**	bluebird bio	Phase III	Beta-globin gene therapy	1,615	New Entry	**4,746**	
17.	**Valoctocogene Roxaparvovec**	BioMarin Pharmaceutical	Phase III	AAV-factor VIII gene therapy	1,318	New Entry	**4,573**	
18.	**Patisiran**	Alnylam Pharmaceuticals	Filed	Transthyretin (TTR) RNAi therapeutic	1,308	New Entry	**4,473**	
19.	**CX-072**	CytomX Therapeutics	Phase II	Anti-programmed cell death ligand-1 (PD-L1) probody	1,153	New Entry	**4,159**	
20.	**Almovig**	Amgen	Filed	Anti-calcitonin gene-related peptide (CGRP) MAb	1,178	New Entry	**4,028**	
	Top 20				34,177		**128,569**	
	Other				178,245		448,421	
	Total				212,422		**576,990**	**13%**
						NPV of R&D Pipeline JUN 2017:	**509,097**	

Do we see any signs of **bolder** innovations from companies leveraging **nano** in current **clinical** studies for cancer?

A Timeline for Cancer Nanomedicine

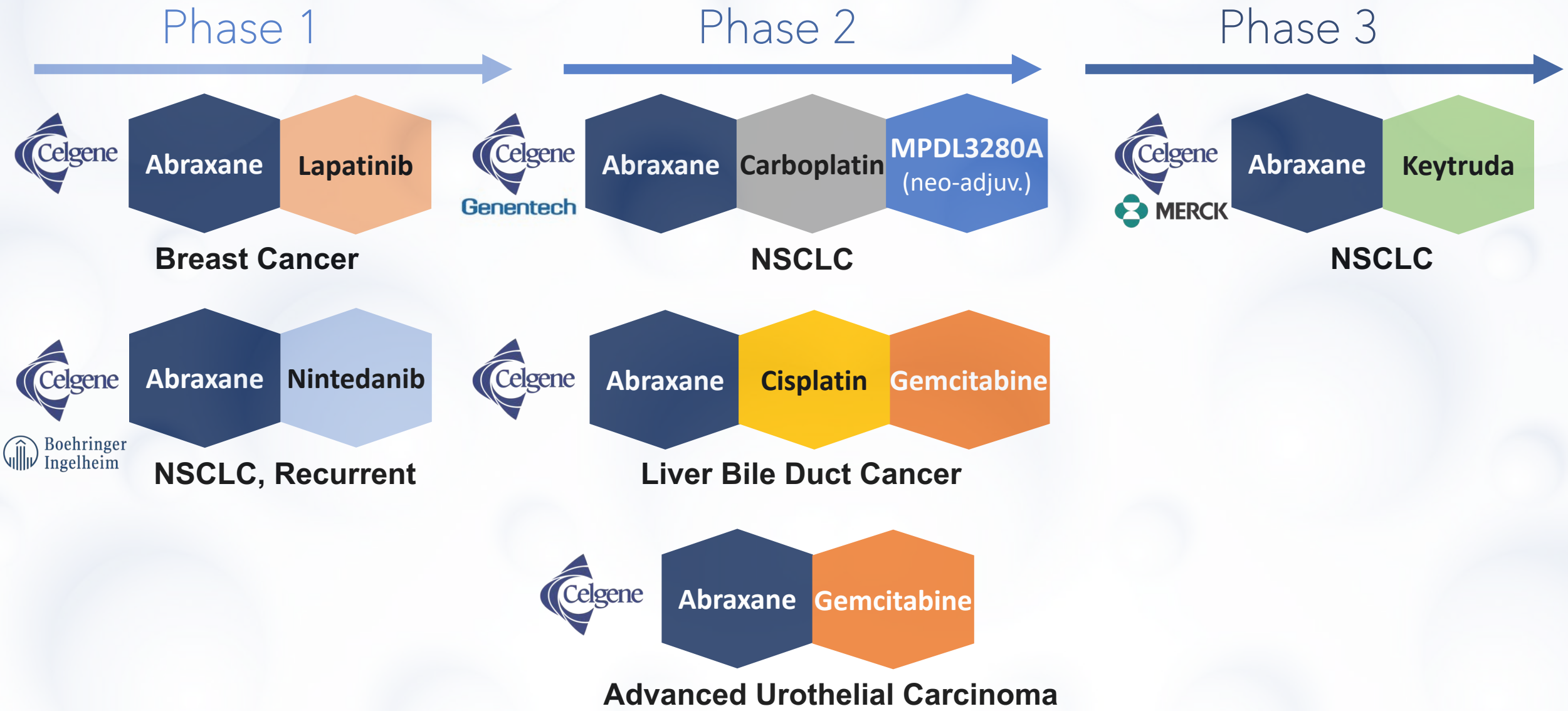


Reference: Shi, J. **Nature Reviews Cancer** (2017)

Current Clinical Trials for Cancer Nanomedicines

- 104 studies currently active using search term "nanoparticle."
- 37 studies sponsored by industry (2 in phase 3, 34 in phases 1-2, 1 in early phase 1)
- Big Pharma: BMS/Celgene, AstraZeneca, Merck, GSK, Boehringer Ingelheim
- Biotechs: Moderna, Nanobiotix, NanoCarrier, Cerulean, Boston Biomedical, Cristal, Genprex, EpiAxis Therapeutics, Nanospectra Biosciences, Aadi, Mina Alpha (liver), Intezyne Technologies, Immix Biopharma, NanOlogy, Corcept Therapeutics, Vasgene Therapeutics, Biomed Valley Discoveries, SCRI Development Innovations, LLC, Actuate Therapeutics, Ipsen, Midatech Pharma, Synergene, Matinas BioPharma Nanotechnologies, Engeneic, Exicure, Torque.

Big Pharma: Doubling Down on Abraxane



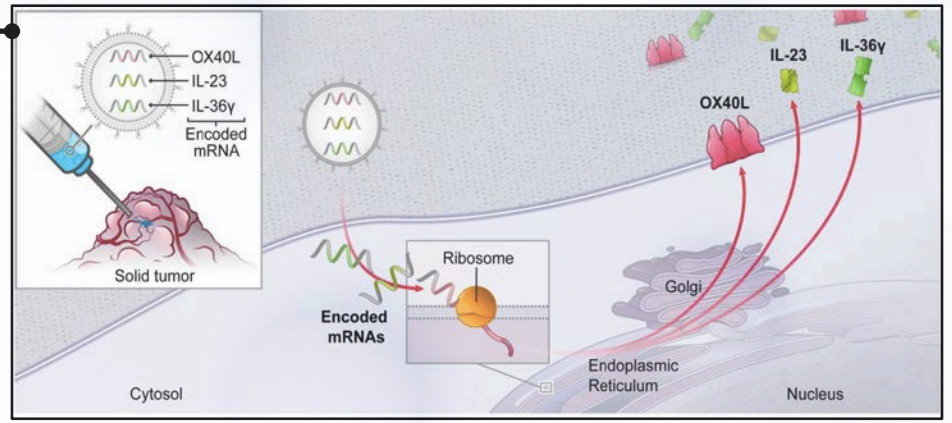
Other Interesting Clinical Trials

moderna

mRNA-2752 (OX40L, IL-23, and IL-36γ) + Durvalumab or Tremelimumab

moderna

mRNA-2416 (OX40L) — **Solid tumors** or **Lymphoma**

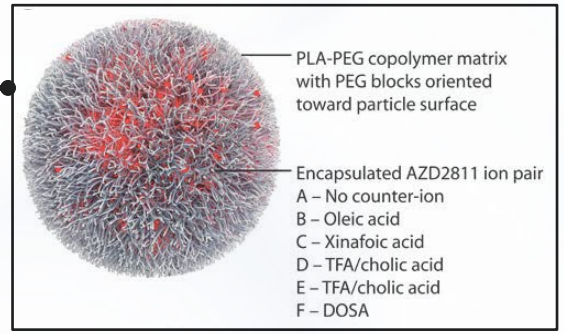


Reference: Hewitt, S. L. **Science Translational Medicine** (2019)

Phase 1

AstraZeneca

AZD2811 (Accurins) + Azacytidine — **Acute Myeloid Leukemia**

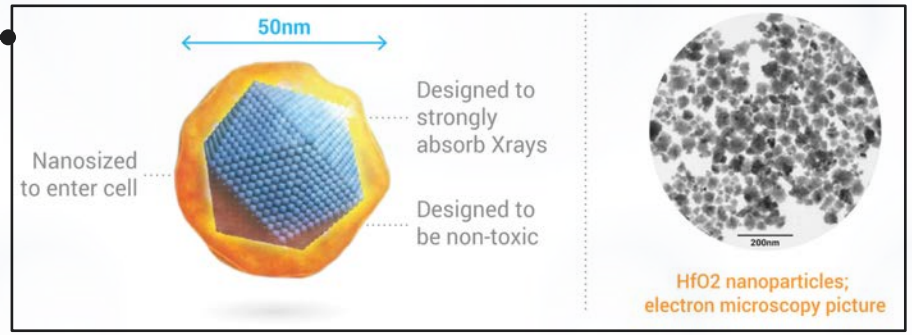


Reference: Ashton, S. **Science Translational Medicine** (2016) and Brugger, W. **Blood** (2017)

Phase 2

NANOBIOTIX

NBTXR3 + radiation therapy — **Soft Tissue Sarcoma**



Reference: Bonvalot, S. **Clinical Cancer Research** (2016)

Phase 3

Discussion Questions

- Question 1: What are some of the biggest challenges facing companies that commercialize nano-enabled platform technologies?

Discussion Questions

- Question 2: Are all these challenges technical?

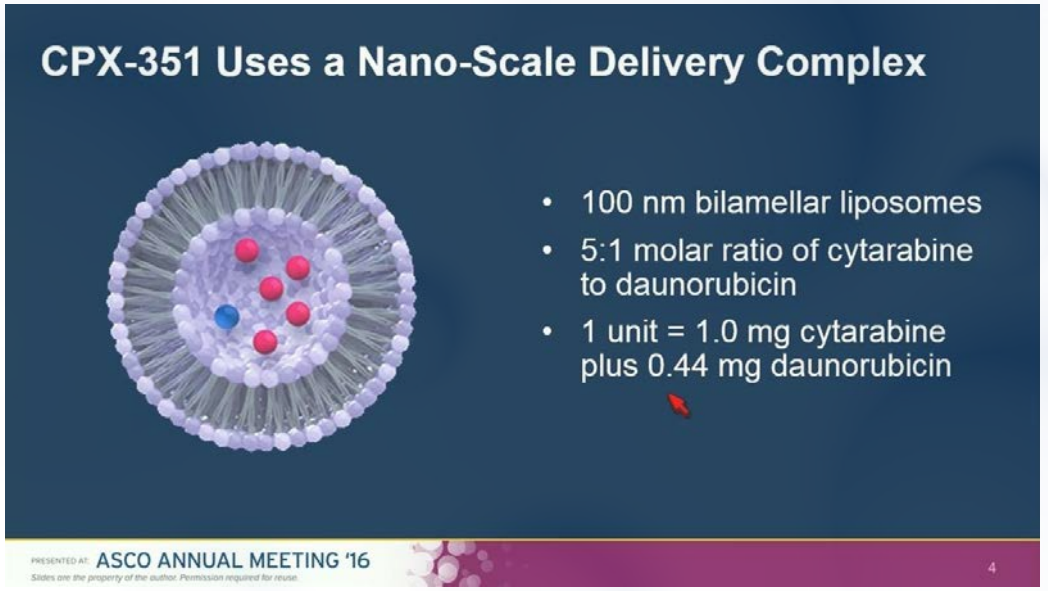
The Case of Vyxeos (Jazz Pharma)

- Ireland-based Jazz Pharma said in its third-quarter 2018 earnings call that sales of Vyxeos were below expectations.
- It lowered its 2018 sales guidance from a range of $115-135 million to $95-110 million, citing several uptake issues like restrictions on usage by healthcare institutions.
- An oncologist specializing in AML who also participated in clinical trials of the drug said some of the reasons likely boil down to its cost and impressions from the physician community.

Vyxeos®

44 mg / 100 mg

Powder for concentrate for solution for infusion



Discussion Questions

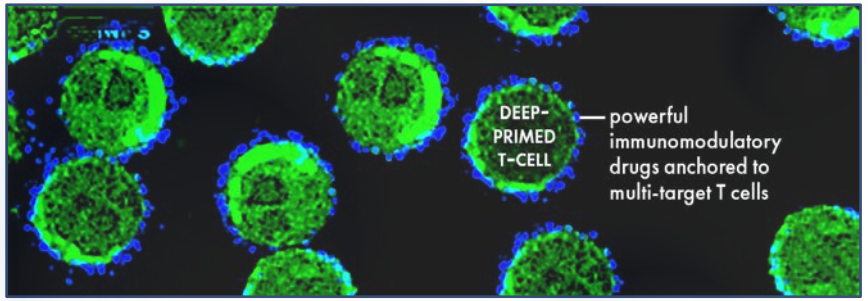
- Question 3: Are you aware of any other active clinical trials involving nanomedicines for treatment/diagnosis of cancer?

Other Exciting "Small" Trials…

exicure

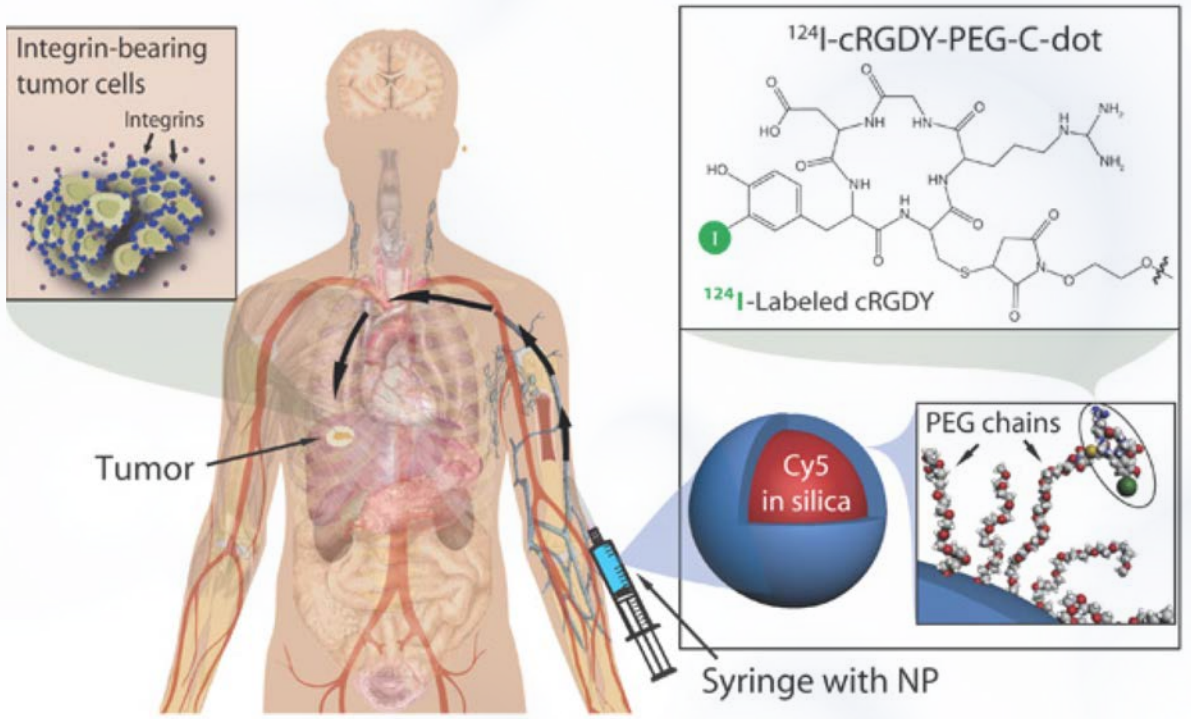
http://exicuretx.com/science-technology/sna-platform.php

TORQUE



http://www.torquetx.com/deep-priming-platform/deep-priming-technology-platform/

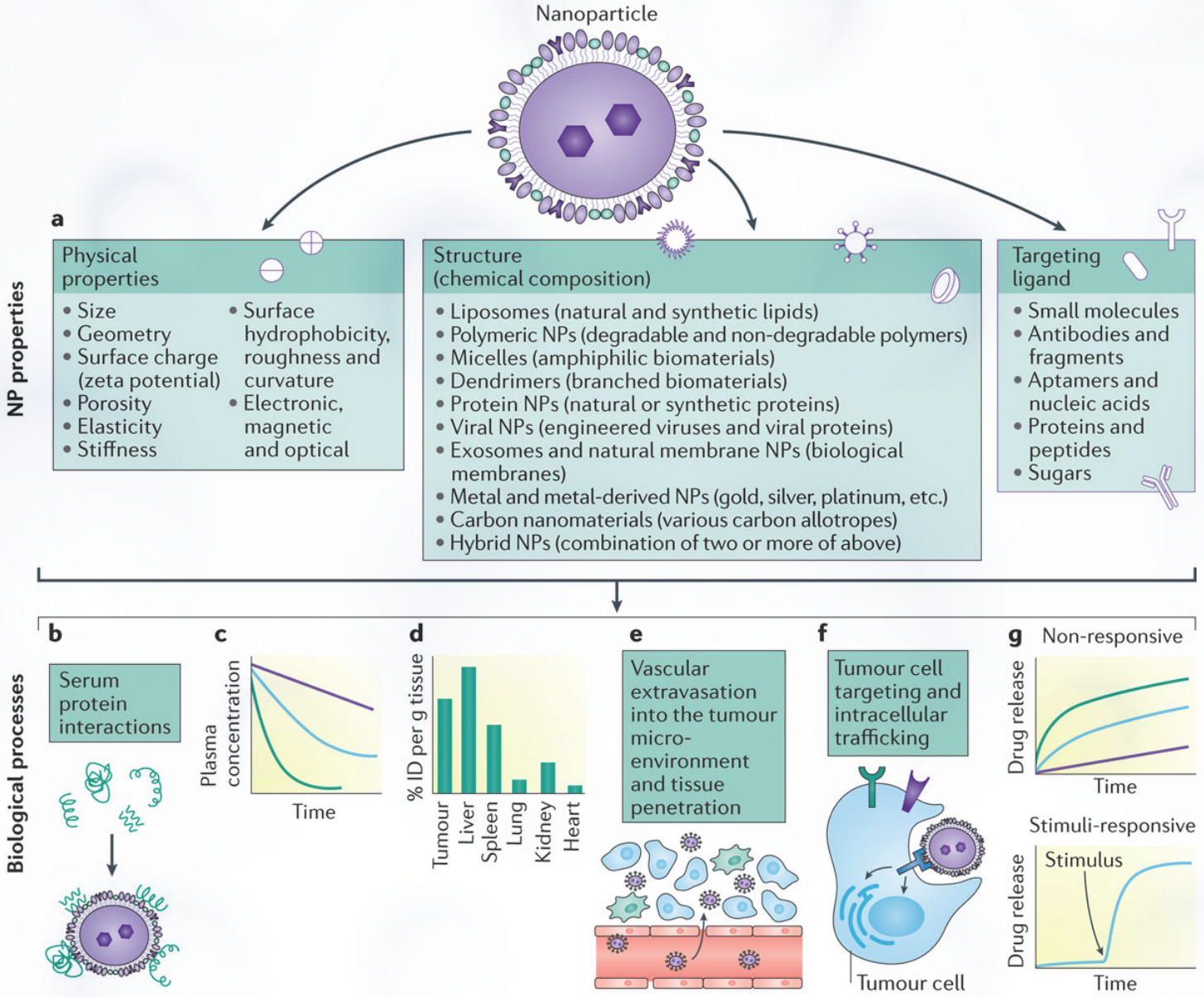
Memorial Sloan Kettering Cancer Center™



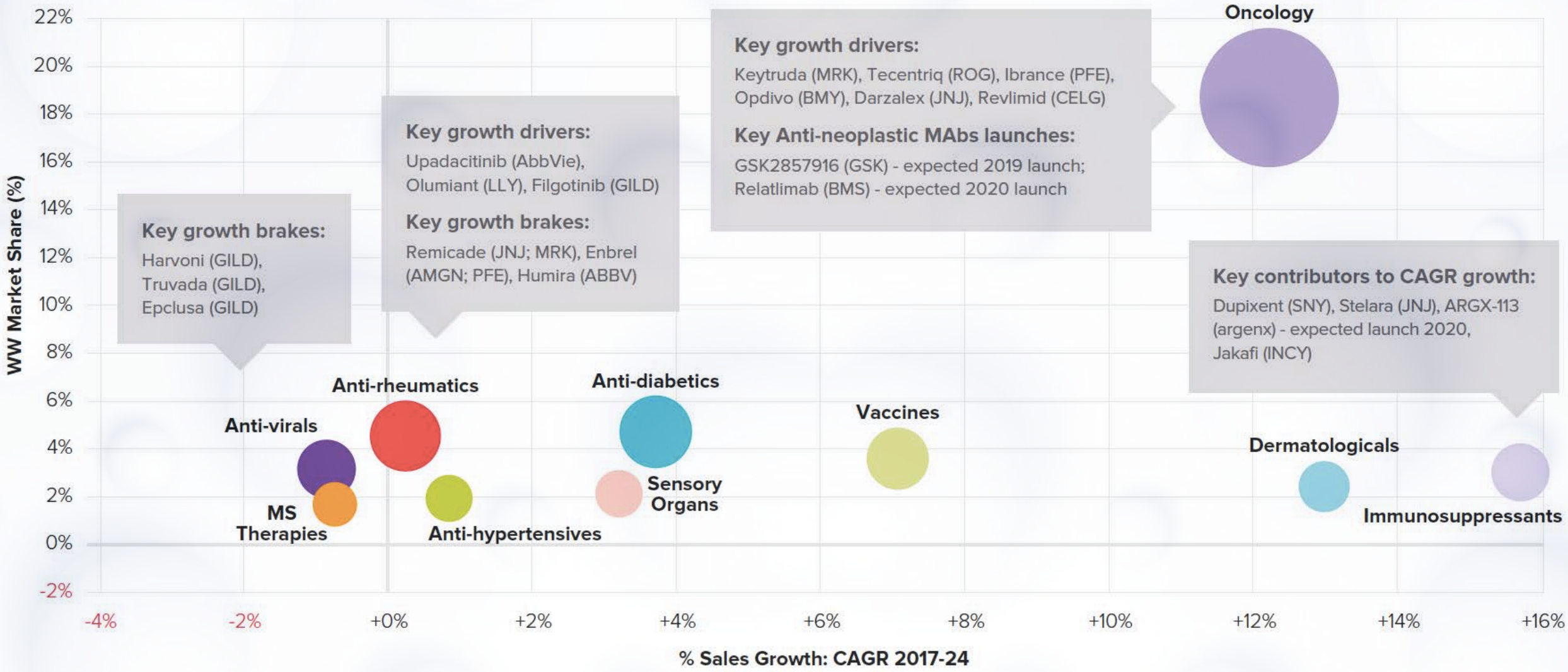
http://stm.sciencemag.org/content/6/260/260ra149

BACK UP

Why Nano?


Nanoparticle
a
NP properties
Physical properties
• Size
• Geometry
• Surface charge (zeta potential)
• Porosity
• Elasticity
• Stiffness
• Surface hydrophobicity, roughness and curvature
• Electronic, magnetic and optical
Structure (chemical composition)
• Liposomes (natural and synthetic lipids)
• Polymeric NPs (degradable and non-degradable polymers)
• Micelles (amphiphilic biomaterials)
• Dendrimers (branched biomaterials)
• Protein NPs (natural or synthetic proteins)
• Viral NPs (engineered viruses and viral proteins)
• Exosomes and natural membrane NPs (biological membranes)
• Metal and metal-derived NPs (gold, silver, platinum, etc.)
• Carbon nanomaterials (various carbon allotropes)
• Hybrid NPs (combination of two or more of above)
Targeting ligand
• Small molecules
• Antibodies and fragments
• Aptamers and nucleic acids
• Proteins and peptides
• Sugars
Biological processes
b
Serum protein interactions
c
Plasma concentration
Time
d
% ID per g tissue
Tumour
Liver
Spleen
Lung
Kidney
Heart
e
Vascular extravasation into the tumour micro-environment and tissue penetration
f
Tumour cell targeting and intracellular trafficking
Tumour cell
g
Non-responsive
Drug release
Time
Stimuli-responsive
Stimulus
Drug release
Time

Top Ten Therapy Areas



Source: EvaluatePharma® World Preview, 2018

Top Ten Therapy Areas

Position 2018 (2017)	Disease	No. of Active drugs 2018 (2017)	Trend
1 (1)	Cancer, breast	727 (654)	↑
2 (2)	Cancer, lung, non-small cell	544 (477)	↑
3 (3)	Cancer, colorectal	503 (476)	↑
4 (6)	Cancer, ovarian	434 (386)	↑
5 (4)	Cancer, pancreatic	430 (416)	↑
6 (5)	Diabetes, Type 2	407 (415)	↔
7 (9)	Cancer, prostate	381 (362)	↑
8 (7)	Alzheimer's disease	381 (376)	↔
9 (10)	Cancer, brain	361 (322)	↑
10 (8)	Arthritis, rheumatoid	352 (372)	↓

Source: EvaluatePharma® World Preview, 2018