THE HONG KONG UNIVERSITY OF SCIENCE AND TECHNOLOGY

IMC INNOVATION MASTER CLASS

HKUST Innovation Master Class

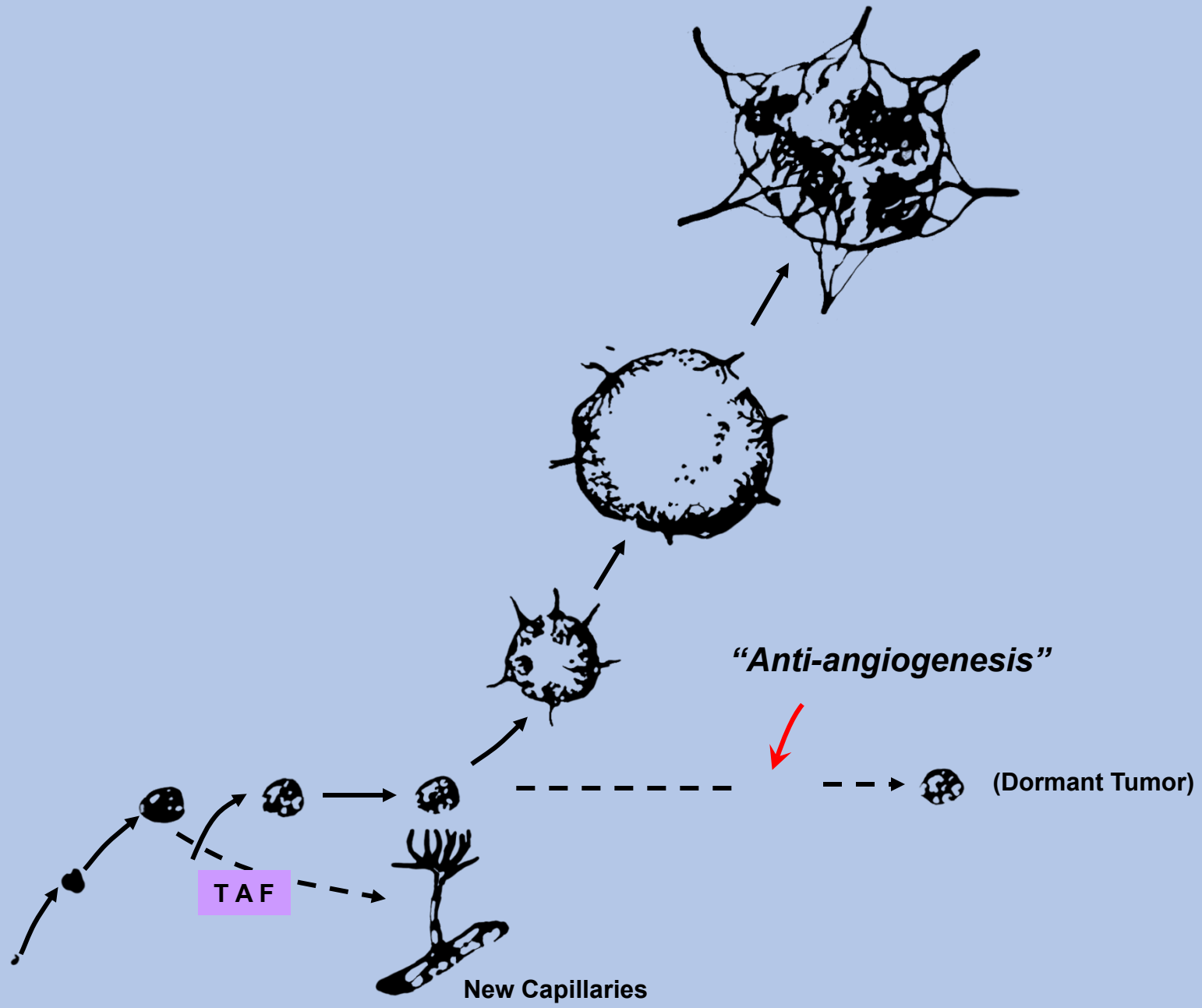
Journey from Science to Innovation

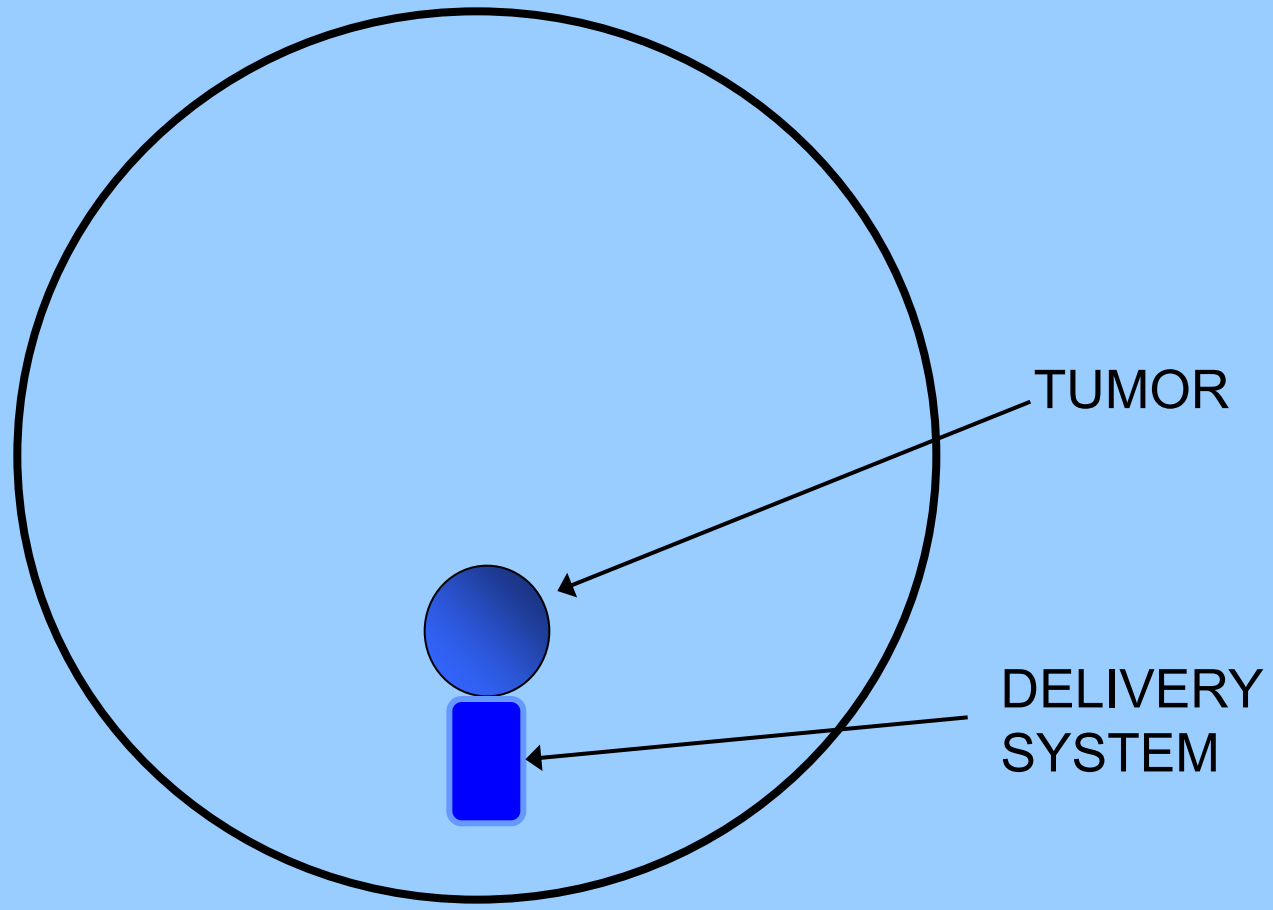
14 November 2024

Journey from Science to Innovation

Dr. Robert S. Langer
Institute Professor
Massachusetts Institute of Technology

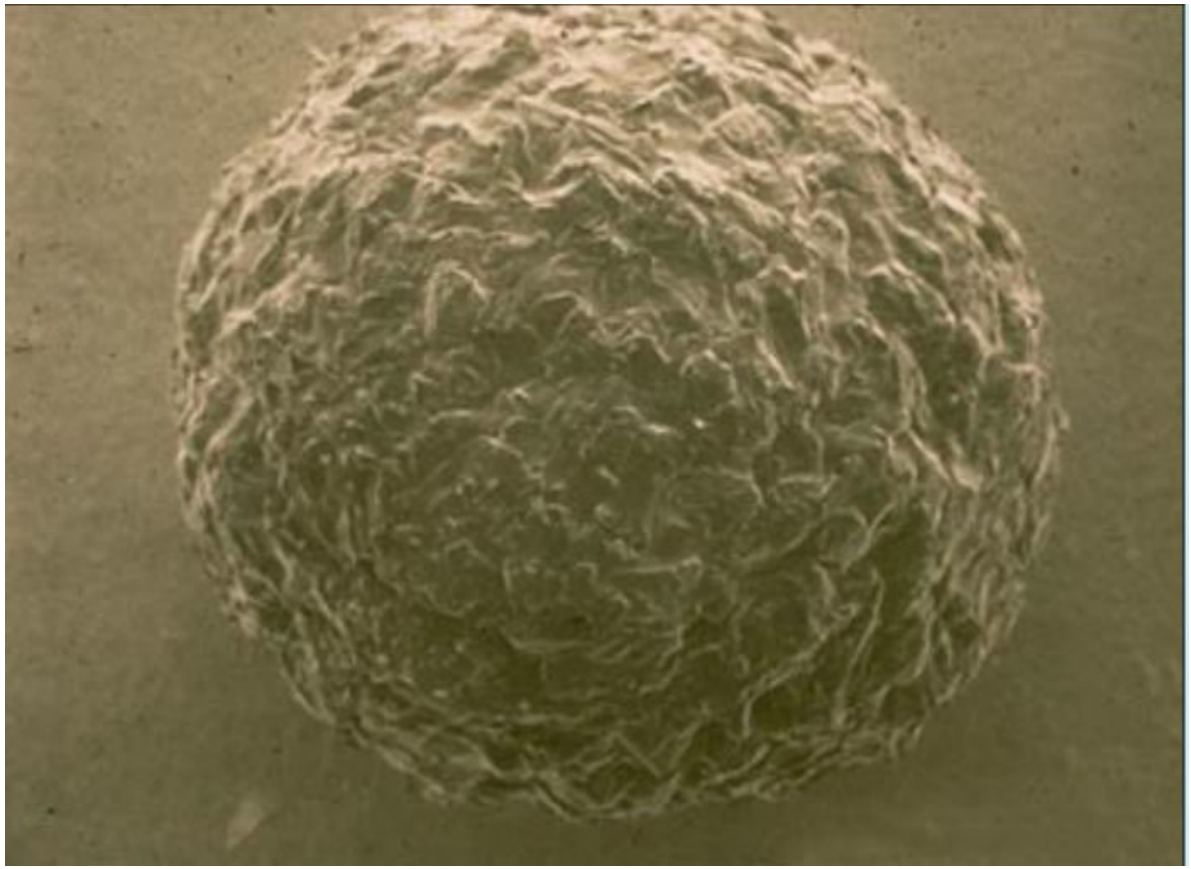
Hong Kong University of Science and Technology
November 14th, 2024

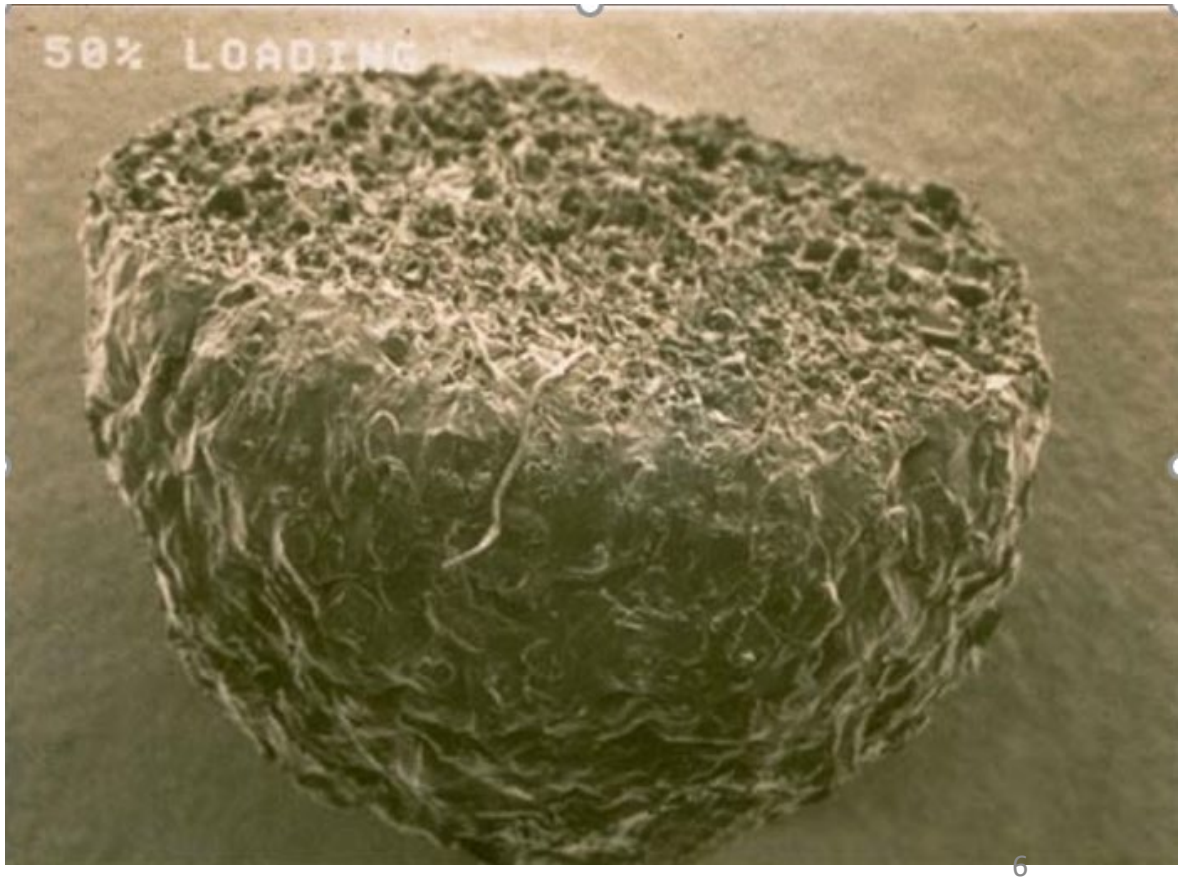

"Anti-angiogenesis"
(Dormant Tumor)
TAF
New Capillaries

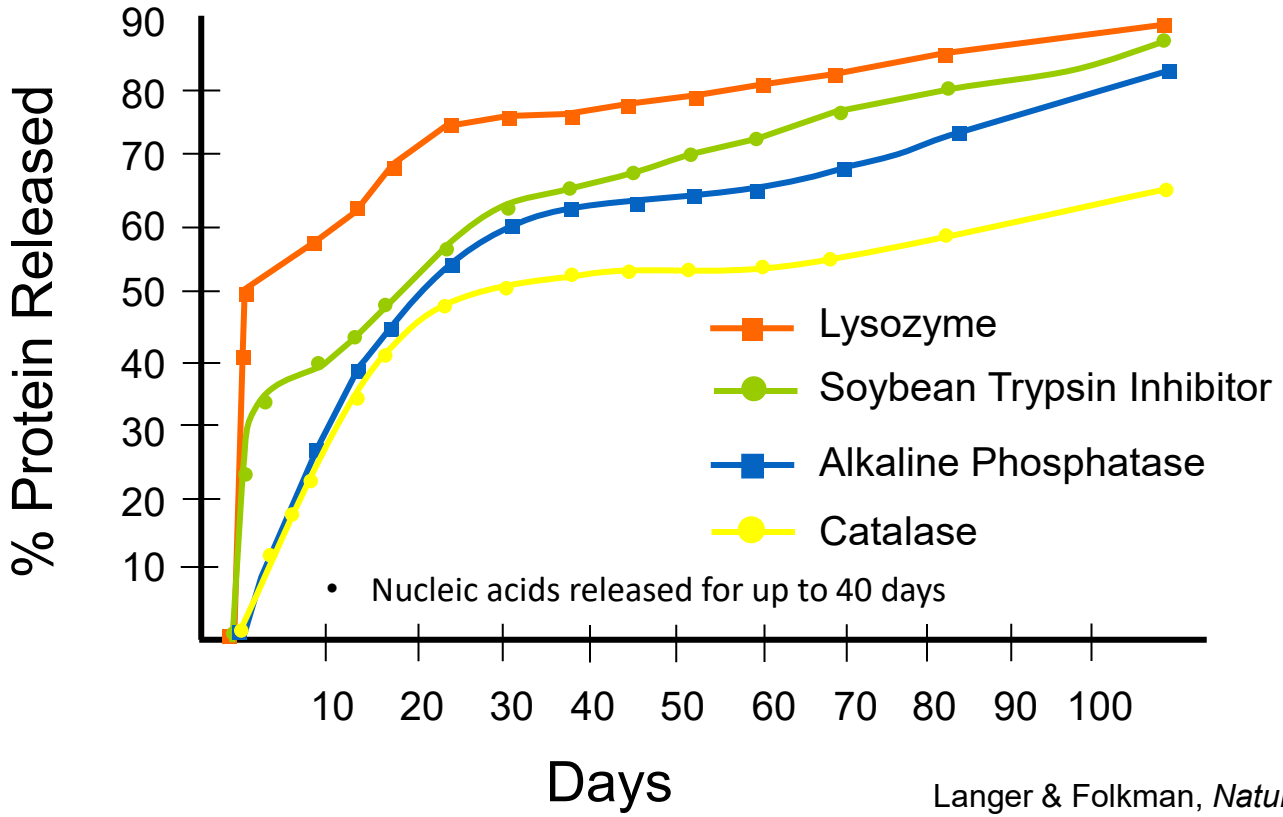

TUMOR
DELIVERY
SYSTEM

This approach ***will not work*** because

Large molecules cannot slowly pass through solid materials




50% LOADING



Langer & Folkman, *Nature,* 1976

nature reviews cancer

Published: 13 June 2023

mRNA-based cancer therapeutics

Chuang Liu *et al.*

nature nanotechnology

Published: 17 March 2023

mRNA therapy at the convergence of genetics and nanomedicine

João Conde *et al.*

References

1.) Langer, R. & Folkman, *Nature,* **263**, 797–800 (1976).

“This work presents the first report of nucleic acids… that can be encapsulated and delivered by tiny particles.”

“Indeed, in 1976, Robert Langer and Judah Folkman were the first to report the use of nano- and microparticles to package nucleic acids such as DNA and RNA[5], raising the possibility of using DNA or RNA as a drug.”

This approach ***will not work*** because

- Large molecules cannot slowly pass through solid materials
- Organic solvents will denature peptides or proteins or nucleic acids

"One evening, I went to a faculty dinner at a Chinese restaurant with Bob Langer and some senior MIT professors. A senior scientist sat quizzing us while smoking a cigar. When the older scientist heard Langer's concepts for … drug delivery, he blew a cloud of smoke in Langer's face and said, 'You better start looking for another job.'"

Professor Michael Marletta
CH and Annie Li Chair in the Molecular Biology of Diseases, University of California – Berkeley
Member, National Academy of Sciences

Angiogenesis inhibitors approved for clinical use

Year Approved	Drug	Disease
2004	Avastin (Bevacizumab)	Colorectal Cancer
2004	Macugen (Pegaptanib)	Macular Degeneration
2005	Nexavar (Sorafenib)	Kidney Cancer
2006	Sutent (Sunitinib)	Gastric (GIST), Kidney Cancer
2006	Lucentis (Ranibizumab)	Macular Degeneration
2007	Nexavar (Sorafenib)	Hepatocellular Carcinoma
2008	Avastin (Bevacizumab)	Breast Cancer
2009	Avastin (Bevacizumab)	Glioblastoma
2009	Votrient (Pazopanib)	Kidney cell carcinoma
2009	Avastin (Bevacizumab)	Kidney Cancer
2011	Sutent (Suntinib)	Gastrointestinal Stromal Tumors
2011	Eylea (Aflibercept)	Macular Degeneration
2012	Inlyta (Axitinib)	Kidney Cancer
2012	Eylea (Aflibercept)	Central Retinal Vein Occlusion
2012	Stivarga (Regorafenib)	Colorectal Cancer
2012	Cometriq (Cabozantinib)	Thyroid Cancer
2012	Zaltrap (ziv-afilbercept)	Metastatic Colorectal Cancer
2013	Avastin (Bevacizumab)	Metastatic Colorectal Cancer
2013	Cyramza (Ramucirumab)	Advanced Stomach Cancer
2013	Stivarga (Regorafenib)	Gastrointestinal stromal cancer
2014	Avastin (Bevacizumab)	Cervical Cancer
2014	Avastin (Bevacizumab)	Recurrent Ovarian Cancer
2014	Cyramza (Ramucirumab)	Non-small Cell Lung Cancer
2015	Lucentis (Ranibizumab)	Diabetic Retinopathy with DME
2017	Lucentis (Ranibizumab)	Diabetic Retinopathy
2017	Mvasi (bevacizumab-awwb)	Metastatic colorectal cancer
2019	Zirabev (bevacizumab-bvzr)	Metastatic colorectal cancer
2020	Avastin (Bevacizumab)	Metastatic hepatocellular carcinoma (HCC) with Tecentriq
2021	Fotivda (Tivozanib)	Renal cell carcinoma
2021	Welireg (Bezultifan)	Pancreatic neuroendocrine tumors, renal cell
2021	Cabozantinib (Cabometyx)	Kidney Cancer
2021	Lenvima (Lenvatinib)	Kidney Cancer
2022	VABYSMO (Faricimab-svoa)	Macular Degeneration
2022	CIMERLI (Ranibizumab-eqrn)	Macular Degeneration
2022	Vegzelma (bevacizumab-adcd)	Colorectal cancer
2022	Beovu (Brolucizumab)	Diabetic macular edema
2022	Alymsy (Bevacizumba-maly)	Metastatic colorectal cancer
2023	LONSURF (Trifluridine and tipiracil with bevacizumab)	Metastatic colorectal cancer
2024	Yesafili (aflibercept-jbvf)	Macular Degeneration
2024	Opuviz (aflibercept-yszy)	Macular Degeneration
2024	Pavblu (aflibercept-ayyh)	Macular Degeneration

"Generally the agent to be released is a relatively small molecule with a molecular weight no larger than a few hundred. One would not expect that macromolecules, e.g. proteins, could be released by such a technique because of their extremely small permeation rates…However, Folkman and Langer have reported some surprising results that clearly demonstrate the opposite."

-Stannett, Koros, Paul, Baker, Lonsdale, *Adv. Poly. Sci.*, 1979.

1983

1st patent issued

U.S. Patent 4,391,797:
Folkman and Langer

"Controlled release of macromolecules"

Enzytech/Alkermes

- 1st 4 employees were former students
- Today, 25 products FDA approved or in clinical trials
- New treatments for schizophrenia, alcoholism, narcotic addiction, diabetes
- ~ 2000 employees


3 mois


Vivitrol

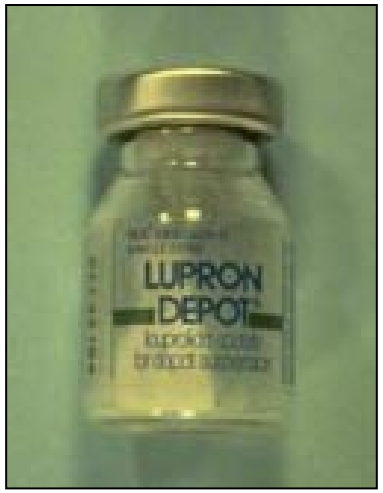

EXPAREL

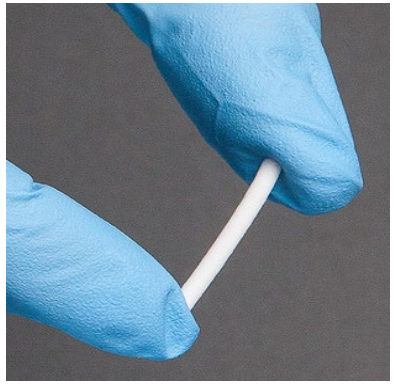

Sydureon™

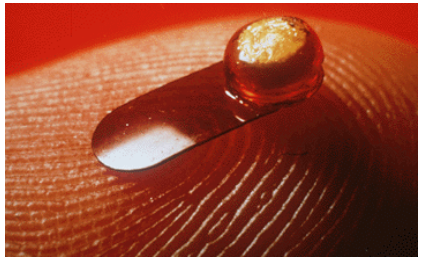

DILUENT FOR NUTROPIN
Nutropin DEPOT

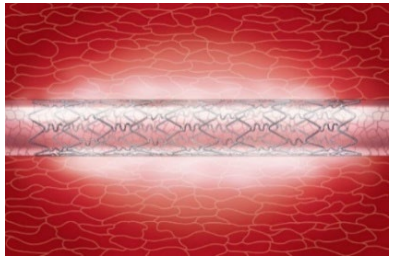

SURGIFLO


Floseal


LUPRON
DEPOT



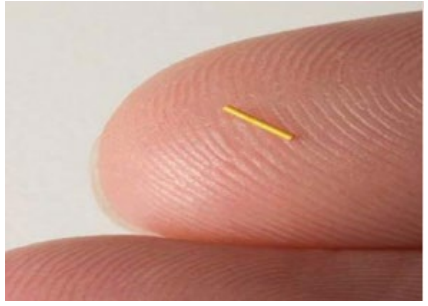





Zoladex 3-month
10.8 mg goserelin


GLIADEL Wafer
(polifeprosan 20 with carmustine implant)
7.7 mg carmustine/wafer


50 mg
37.5 mg
25 mg
RisperdalCONSTA
DOSE PACK CONTENTS:



Biomolecules

- Proteins – Monodisperse
- Nucleic acid (e.g. DNA) – Monodisperse
- Polysaccharides – Polydisperse

Mission

Harness glycomics towards improving existing therapies and develop novel therapeutics for human diseases

Approach to finding glycoforms

- Fractionate to find the right glycoform

- The 1st sequencing approach to complex polysaccharides (Sasisekharan, Venkataraman, Science, 1999) uses molecular scissors (Langer, Science, 1982)

Potential products

- Heparins
- Other complex polymers
- New glycoproteins

Momenta

2001	Started with 2 former students *(Ram Sasisekharan & Ganesh Venkataraman)*
2004	Goes public
2003 & 2006	Major investment by Novartis
2010	1st Lovenox biogeneric approved by FDA *(The 1st complex drug approved based on analytic data; Largest syringe launch in history)*
2011	Major investment by Baxter
2015	Capoxone approved by FDA
2016	Major investment by Mylan
2017	Major Investment by CSL
2020	Johnson & Johnson acquires Momenta for $6.5B USD


NDC 0781-3119-63
Enoxaparin Sodium Injection
30 mg/0.3 mL (100 mg/mL)
Single Dose Syringes with Automatic Safety Device
For Subcutaneous Injection
℞ only
Ten 0.3 mL Syringes
0781-3119-63
SANDOZ
NDC 0781-3119-64
Enoxaparin Sodium Injection
40 mg/0.4 mL (100 mg/mL)
Single Dose Syringes with Automatic Safety Device
For Subcutaneous Injection
℞ only
Ten 0.4 mL Syringes
0781-3119-64
SANDOZ

Momenta Pharma soars on landmark FDA approval

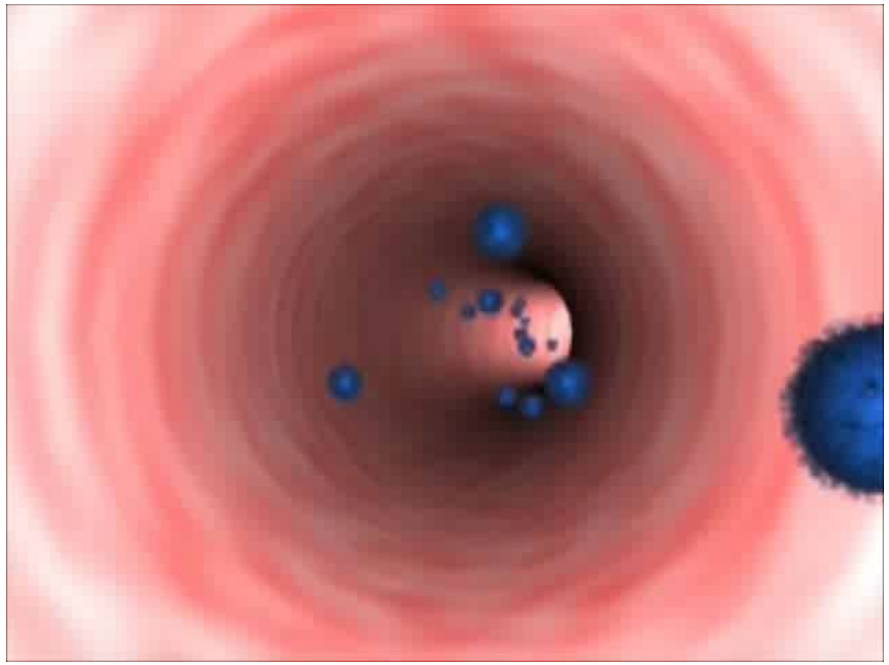
July 23, 2010

The gene medicine bottleneck: Delivery

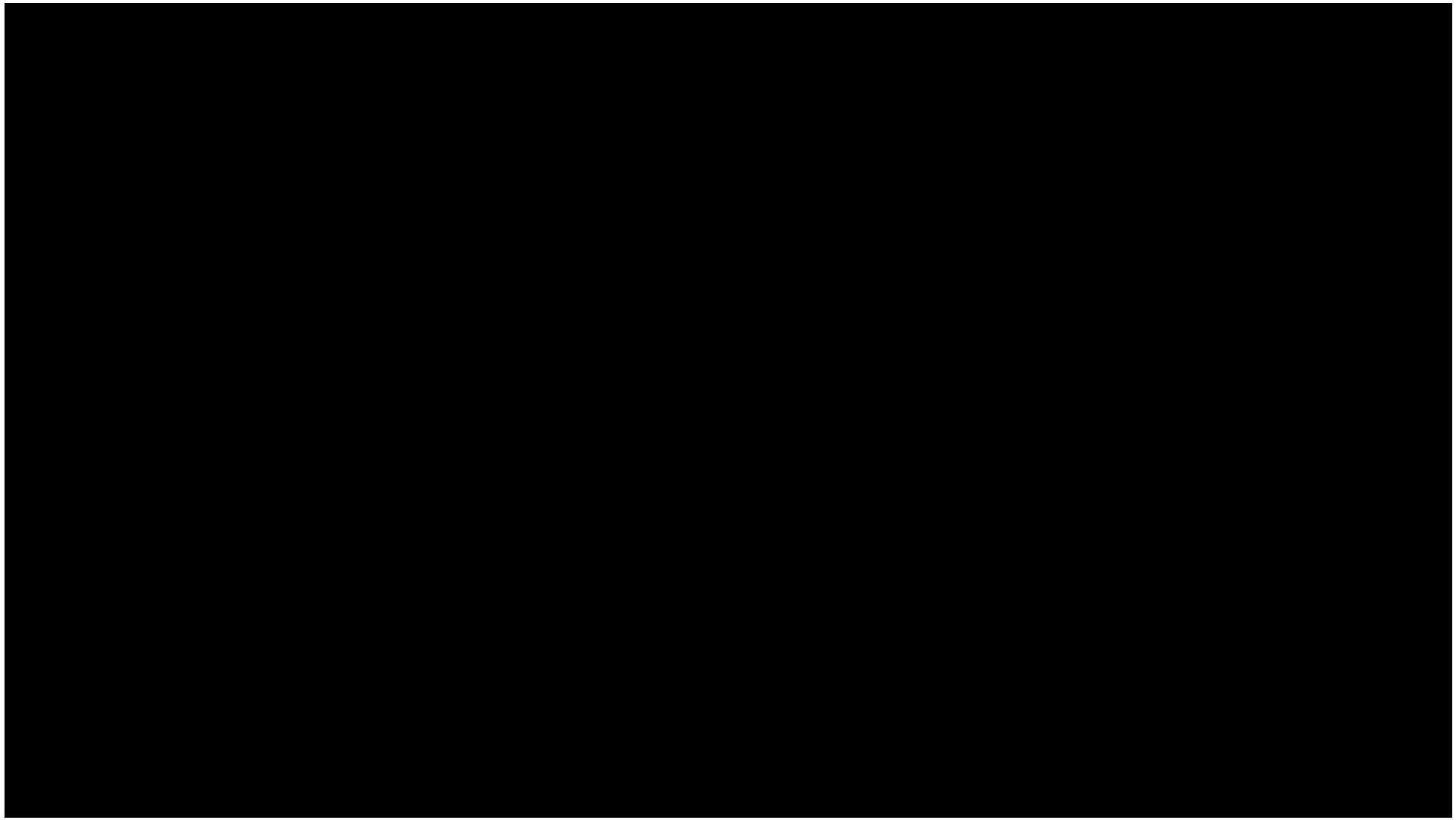
"There are only three problems in gene therapy: delivery, delivery, and delivery."

—Inder Verma, 1999

"We need to solve the delivery problem"



—Phil Sharp 2007



Small molecules

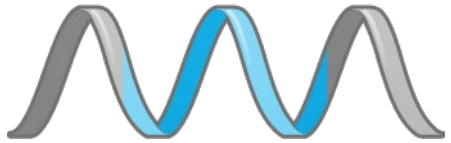
Genetic therapy (e.g., siRNA, mRNA)

Central Dogma of Molecular Biology

DNA

Hard Drive
DNA stores our genetic information

messenger RNA



Software
mRNA reads off the DNA and instructs cells to make protein

Protein

Hardware
Proteins accomplish the work in the body – structure, signaling, metabolism, etc.

Delivery of nucleic acids from tiny particles, Nature, 263: 797-800, 1976.

PEG coatings, Science, 263: 1600-1603, 1994.

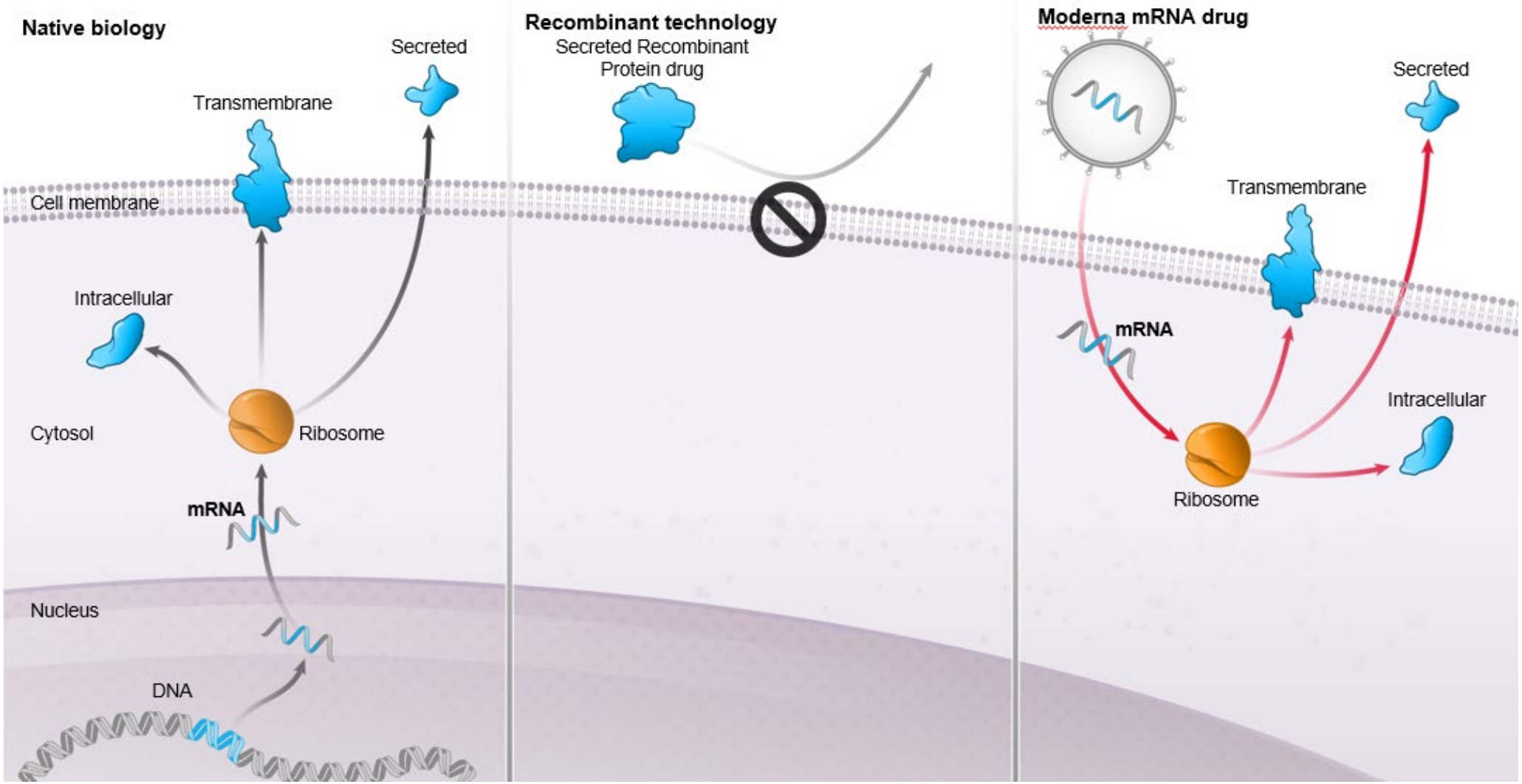
Ionizable components. Biotechnology and Bioengineering, 67: 217-223, 2000.

Proceedings of the National Academy of Sciences, 98: 3, 1200-1205, 2001.

Large Numbers of Ionizable lipids, Nature Biotechnology, 26: 561-569, 2008

Microfluidic Manufacturing of Drug Delivery Nanoparticles, Nano Letters, 8: 2906-2912, 2008

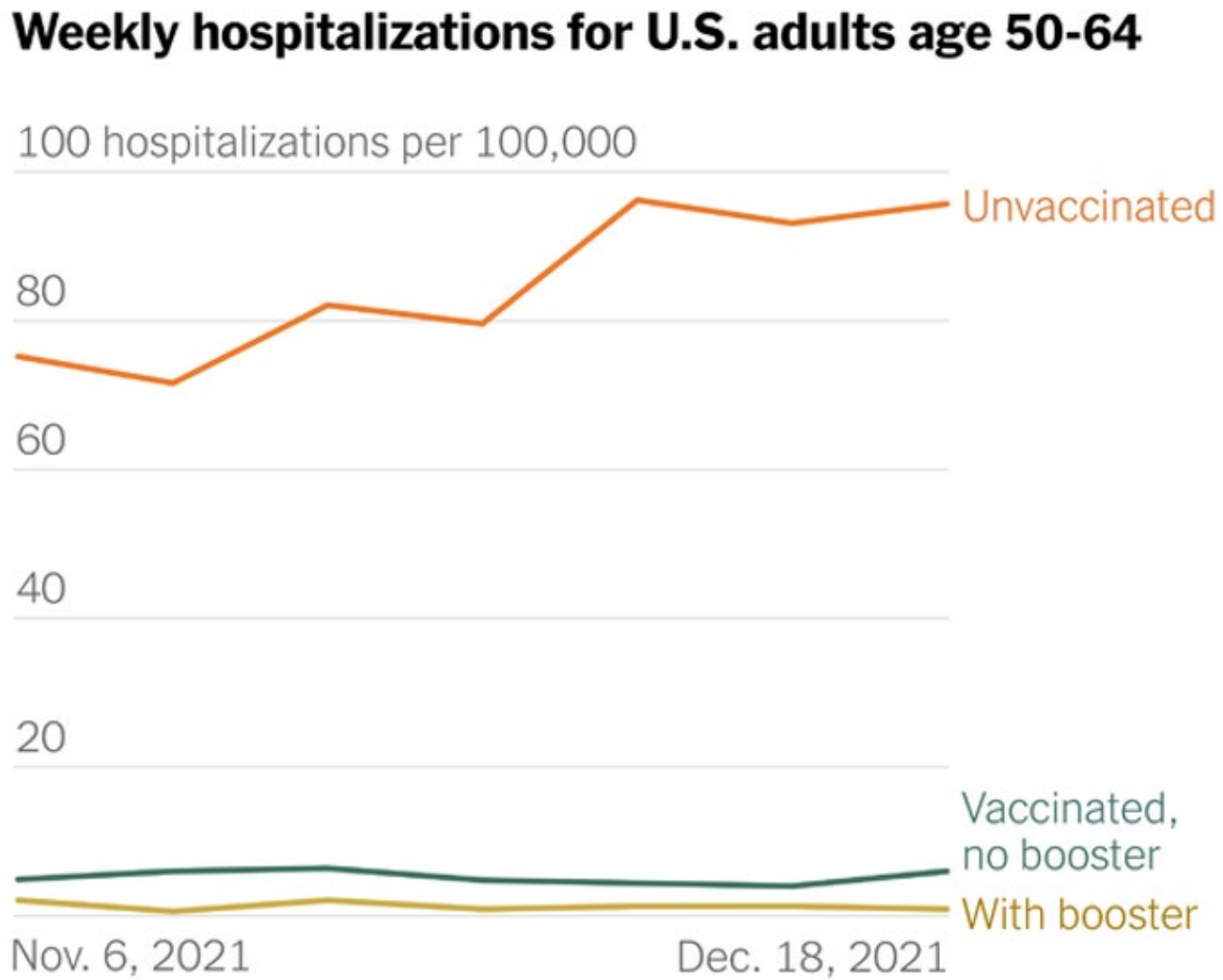
If mRNA could be a drug… it would enable new intra-cellular and membrane-bound proteins



Moderna Covid Vaccine Timeline

January 11, 2020	Chinese scientists publish virus genetic sequence
January 13, 2020	Finalize messenger mRNA vaccine design
February 24, 2020	Ship vaccine batches to NIH for testing
March 16, 2020	1st dose in humans (Seattle, WA)


Moderna COVID-19
Vaccine
0.20 mg/mL Suspension for
COVID-19 mRNA
Intramuscular Use
Multiple-dose vial
(10 doses of 0.5 mL)



Based on data from 14 U.S. jurisdictions. | Source: Centers for Disease Control and Prevention

Vaccine effectiveness (Mayo Clinic 2/1/22)

- Moderna 94 percent
- Pfizer/ BioNtech 91 percent
- Johnson and Johnson 66 percent (removed from US Market).

BROWN | News from Brown

Moderna is safest, most effective mRNA vaccine against COVID-19 for older adults, study shows

Reference: *Journal of American Medical Association Network Open*
August 2, 2023

6,388, 196 patients
Average age: 76.3 years

Efficacy — Moderna's vaccine had a 15% lower risk of diagnosed Covid-19 compared to Pfizer-BioNtech

Both are more effective than any other vaccine

Safety — Moderna's vaccine had fewer side-effects, e.g.:
4% lower risk of pulmonary embolism compared to Pfizer-BioNtech
2% lower risk of thromboembolic events compared to Pfizer-BioNtech

Received: 17 September 2021 | Accepted: 26 October 2021
DOI: 10.1002/jmv.27424

RESEARCH ARTICLE

JOURNAL OF MEDICAL VIROLOGY WILEY

Comparative safety of mRNA COVID-19 vaccines to influenza vaccines: A pharmacovigilance analysis using WHO international database

- 18, 755 and 27, 895 individuals who reported to VigiBase….respectively, from January 1, 2020 to January 17, 2021

- The overall safety profile showed a lower risk of serious Adverse Events Following Immunization (AEFI) following mRNA vaccines compared to the influenza vaccines.

Kim MS, Jung SY, Ahn JG, et al. Comparative safety of mRNA COVID-19 vaccines to influenza vaccines: A pharmacovigilance analysis using WHO international database. *J Med Virol.* 2022; 94:1085-1095. doi:10.1002/jmv.27424 KIM ET AL.

U.S. Covid Treatments

(as of March 16, 2023)

Vaccines	**49 failed vaccines**	**2 approved vaccines**
Treatments	**209 failed treatments**	**1 approved treatment**
Antivirals	**153 failed antivirals**	**1 approved antiviral**

Source: *Forbes (March 2023)*

As of March 16, 2023, Commonwealth Fund (U.S.) estimates that the vaccine

- **Prevented 3,000,000 deaths due to Covid**
- **Prevented over 18,000,000 hospitalizations**
- **Prevented almost 120,000,000 Covid infections**
- **Saved the U.S. $1,500,000,000,000 USD in medical costs**

Individualized Neoantigen Therapies (Personalized Cancer Vaccines)

- 157 patients with stage III/IV melanoma

- Pcv—Select up to 34 mutations known as neoepitopes in patient cancer cells. Incorporate the genetic code of these neoepitopes into mRNA vaccine the same way it was done for COVID vaccines (i.e. mRNA in nanoparticles)

- Randomized double-blind trial
  - Half got Keytruda
  - Half got Keytruda plus pcv

- At 2 years, risk of recurrence or death reduced by 44% (one-sided p value=0.0266)

- At 3 years, the risk of recurrence or death reduced by 49% (one-sided p-value = 0.0095.)

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