Transforming Science into Impactful Innovations: Lessons in Entrepreneurship

8 Nov 2021
Medicon Valley Alliance

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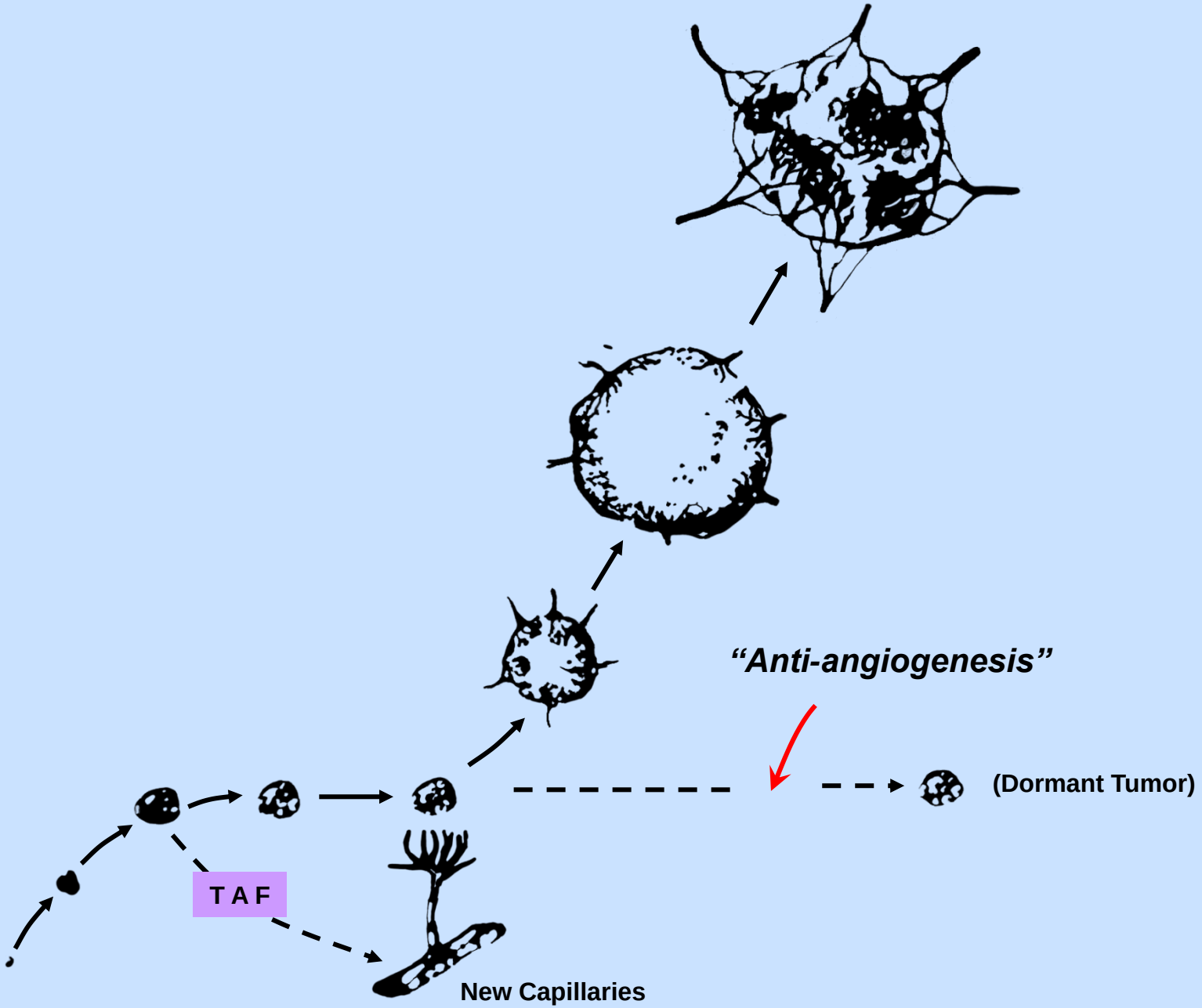
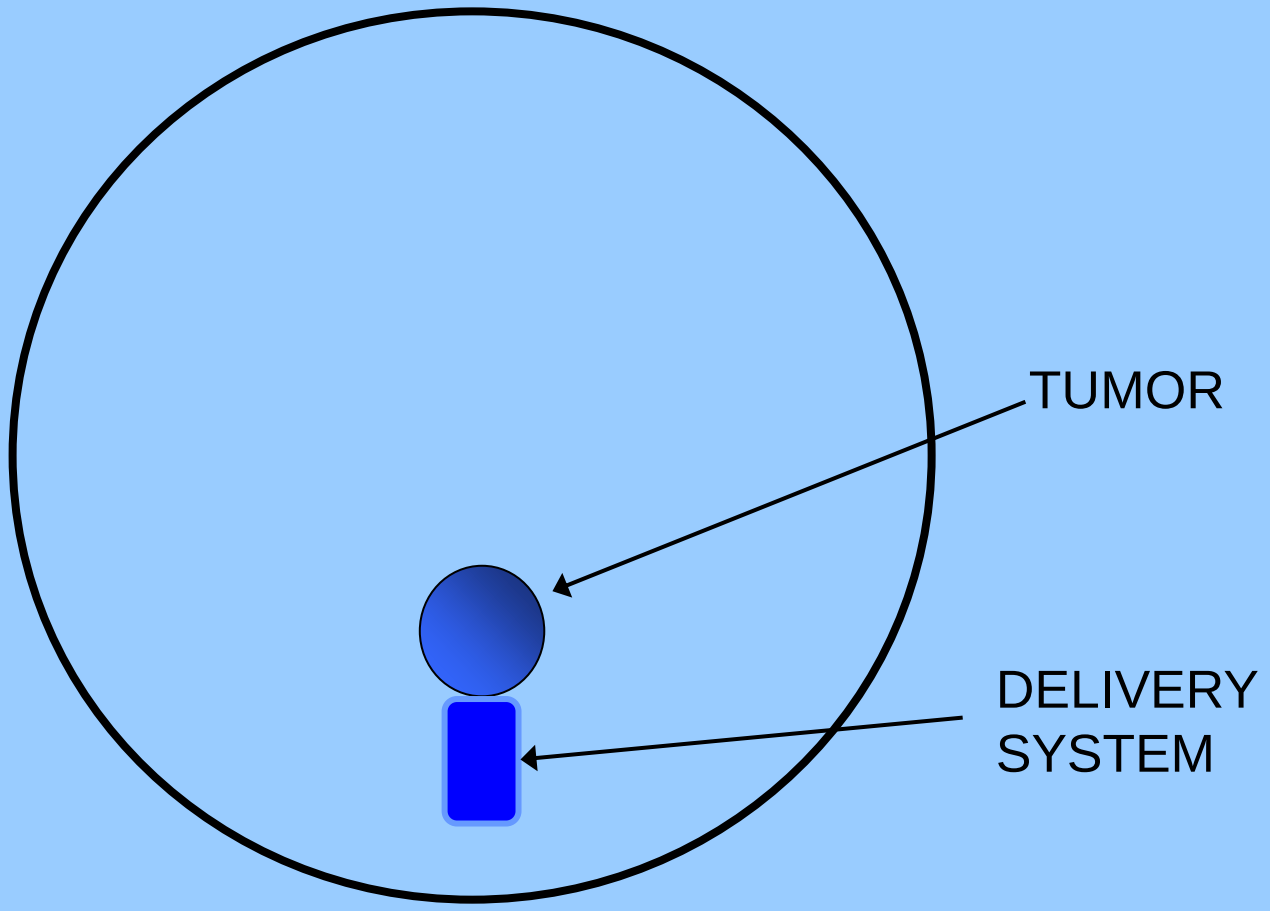
Institute Professor
Massachusetts Institute of Technology

Innovation

- Do things that you hope will have very big impact (as opposed to incremental research)
- Conventional wisdom isn't always correct
- Exposure to very different disciplines
- Take risks (failure is OK)
- If your idea is important, expect lots of criticism
- Never give up (Almost)


"Anti-angiogenesis"
(Dormant Tumor)
T A F
New Capillaries

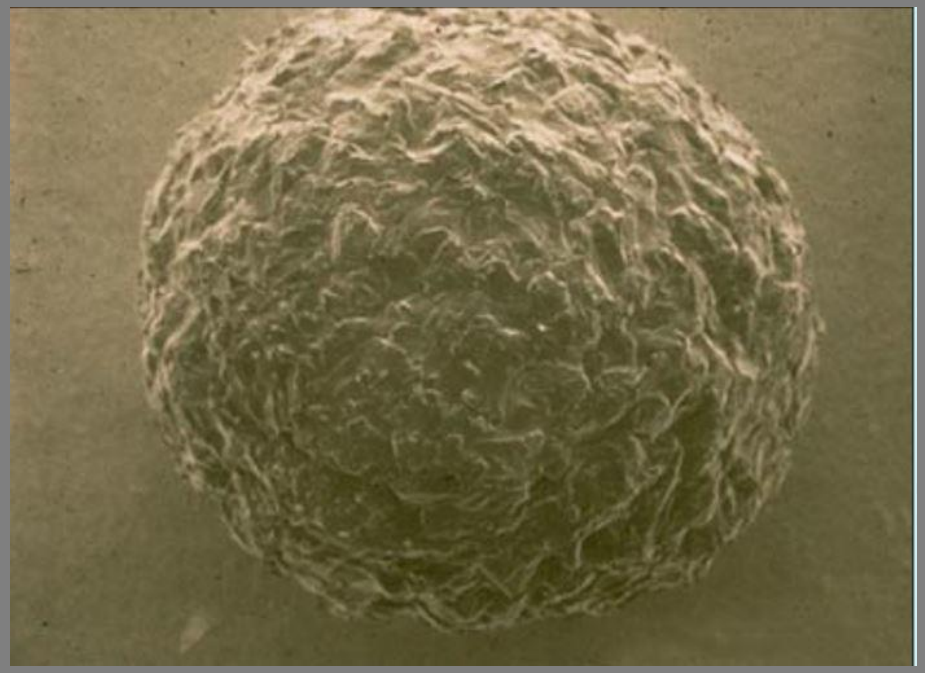

TUMOR
DELIVERY
SYSTEM

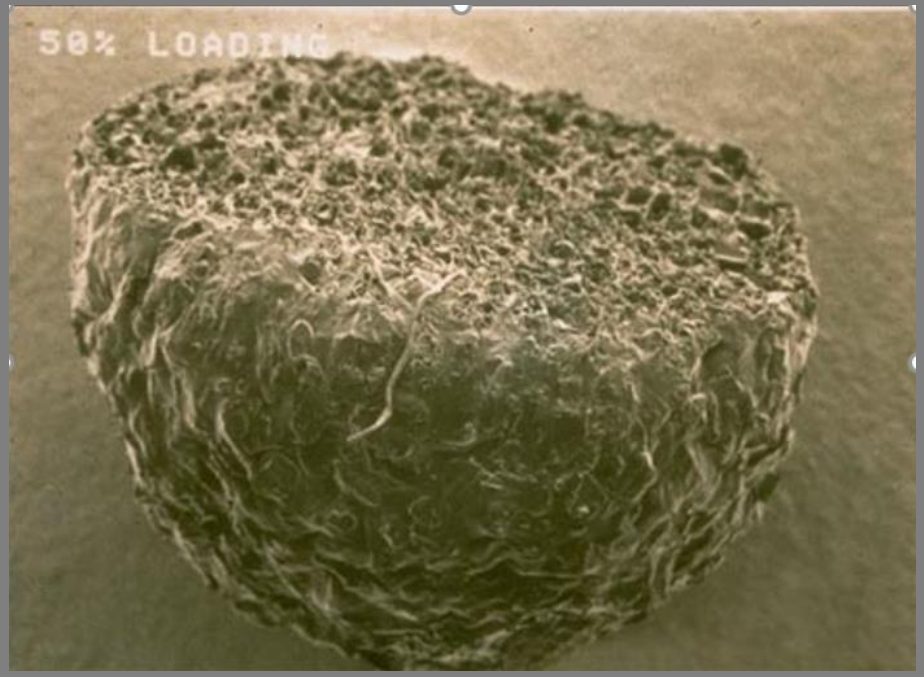
This approach will not work because

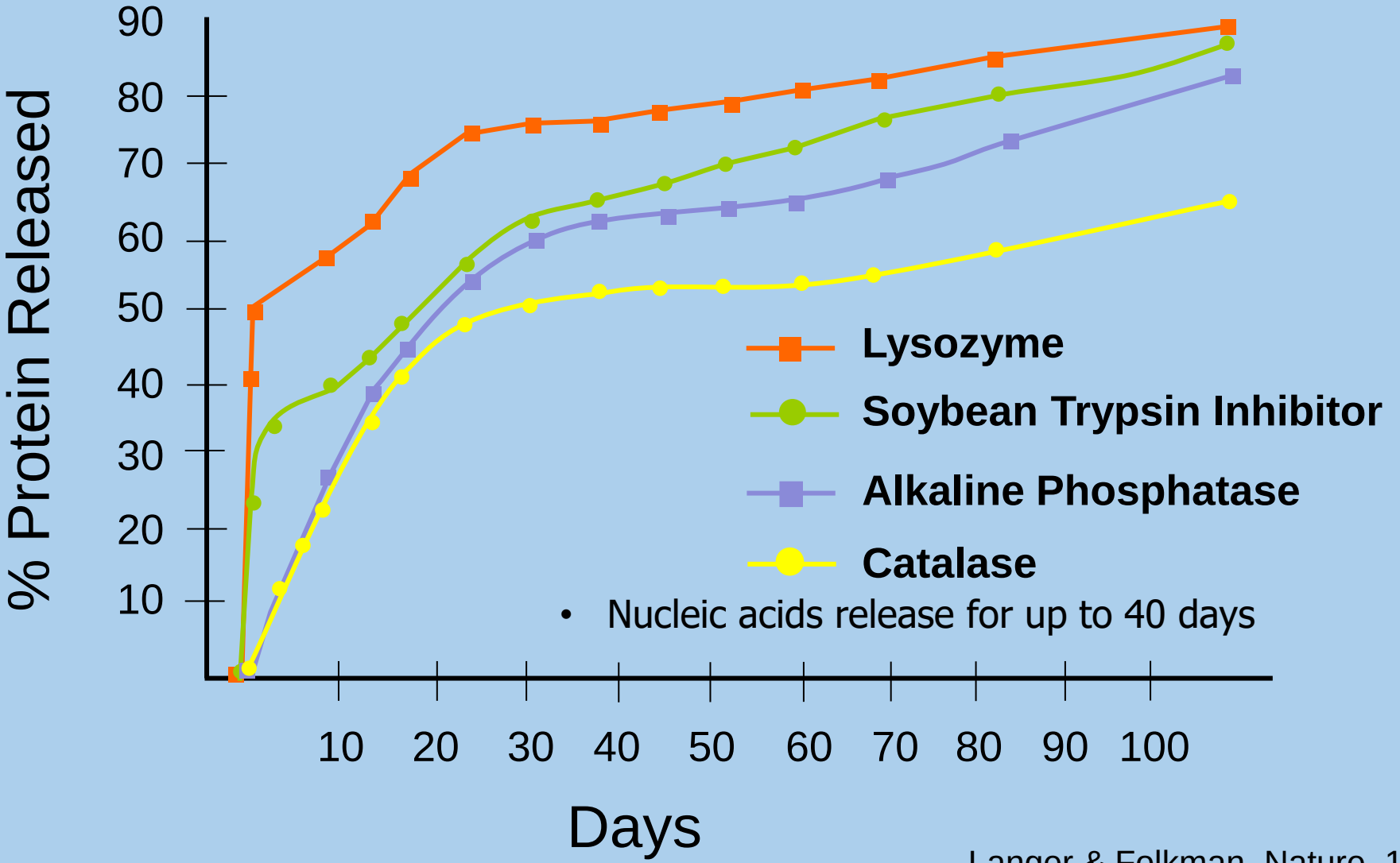
Large molecules cannot slowly diffuse through solid materials

“The use of polymer matrices for slow release systems has been virtually restricted to small molecules.”

---*Chemical and Engineering News*, 1977




50% LOADING



Langer & Folkman, Nature, 1976

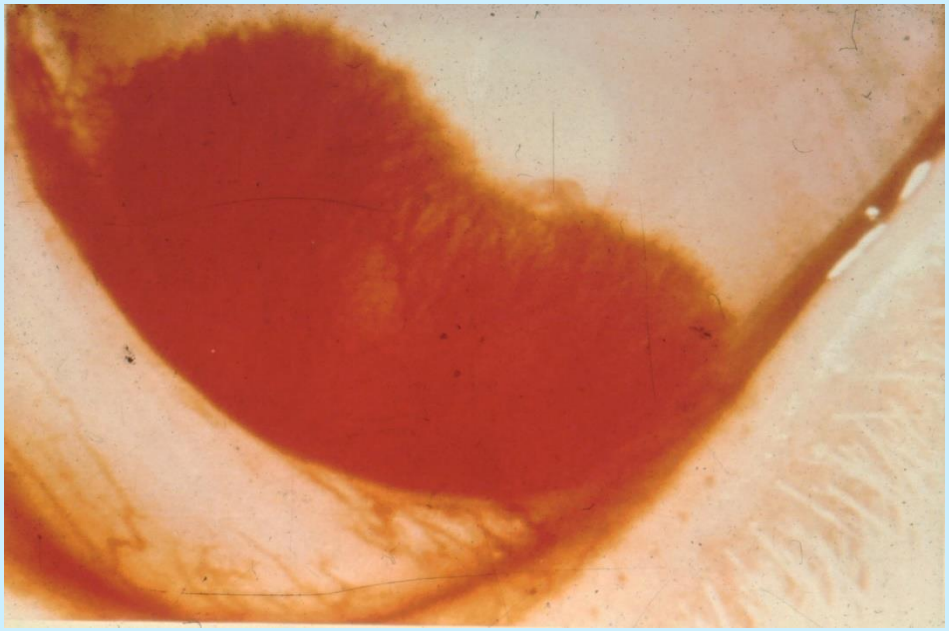
This approach will not work because

- Large molecules cannot slowly diffuse 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

Rabbit corneal pocket assay



-CDI

+CDI

Langer et al, *Science*, 1976

Angiogenesis inhibitors approved for clinical use

Date Approved	Drug	Disease
February 2004	Avastin (Bevacizumab)	Colorectal Cancer
November 2004	Tarceva (Erlotinib)	Lung Cancer
December 2004	Macugen	Macular Degeneration
December 2005	Nexavar (Sorafenib)	Kidney Cancer
December 2005	Revlimid	Myelodysplastic Syndrome
January 2006	Sutent (Sunitinib)	Gastric (GIST), Kidney Cancer
June 2006	Lucentis	Macular Degeneration
May 2007	Torisel (CCI-779)	Kidney Cancer
November 2007	Nexavar (Sorafenib)	Hepatocellular Carcinoma
February 2008	Avastin	Breast Cancer
May 2009	Avastin	Glioblastoma
November 2010	Afinitor	Giant Cell Astrocytoma
April 2011	Zactima (Vandetanib)	Medullary Thyroid Cancer
May 2011	Sutent	Pancreatic Neuroendocrine Tumors
November 2011	Eylea (Aflibercept)	Macular Degeneration
January 2012	Axitinib (AG-013736)	Kidney Cancer
July 2012	Afinitor	Breast Cancer
September 2012	Eylea (Aflibercept)	Central Retinal Vein Occlusion
January 2013	Avastin	Metastatic Colorectal Cancer
February 2013	Pomalyst (Pomalidomide)	Multiple Myeloma
April 2014	Cyramza	Advanced Stomach Cancer
August 2014	Avastin (Bevacizumab)	Cervical Cancer
November 2014	Avastin	Recurrent Ovarian Cancer
December 2014	Cyramza (Ramucirumab)	Non-small Cell Lung Cancer
February 2015	Lucentis	Diabetic Retinopathy with DME
February 2015	Lenvima (Lenvatinib)	Thyroid Cancer
April 2017	Lucentis	Diabetic Retinopathy
June 2020	Avastin	Metastatic hepatocellular carcinoma (HCC) with Tecentriq

"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, opioid addiction, diabetes
- ~ 2000 employees


Decapeptyl LP 11.25
3 mois


Vivitrol


EXPAREL

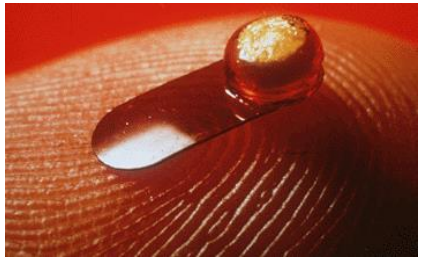

Hydureon


DILUENT FOR NUTROPIN
Nutropin Depot


SURGIFLO


Floseal

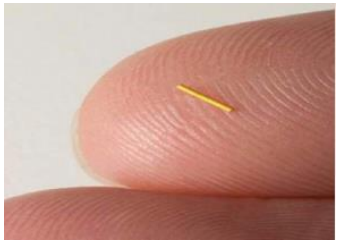

LUPRON DEPOT

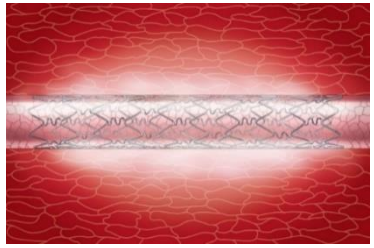



Zoladex 3-month
10.8 mg goserelin


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


50 mg
37.5 mg
25 mg
RisperdalCONSTA






Forteo

Biomolecules

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

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

Heparin crisis

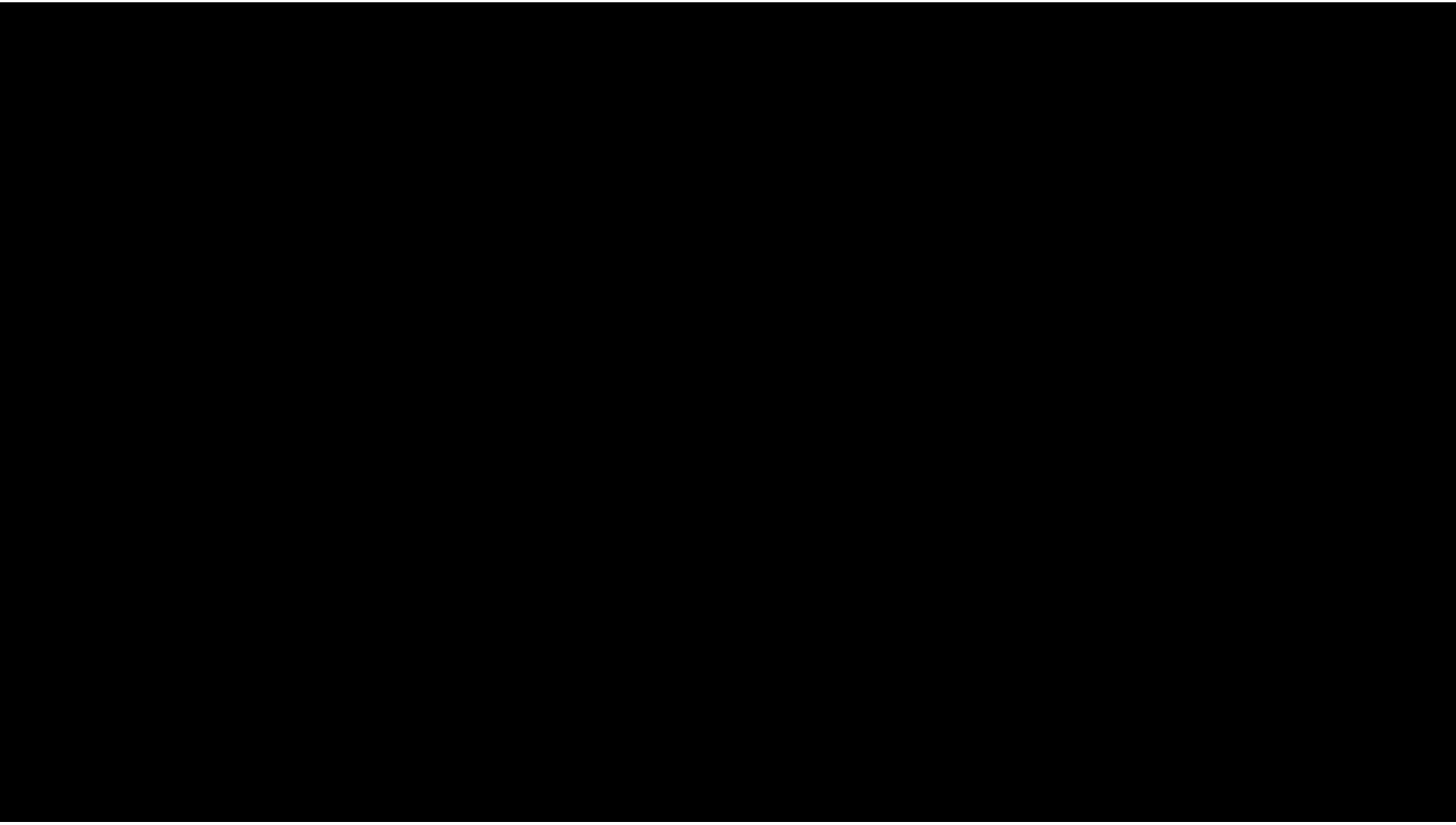
- Problems found at Chinese heparin plant
  Seattle Times, February 29, 2008
- More heparin recalled because of contamination
  Associated Press, March 22, 2008
- Heparin recall tally spreads to six countries
  MedPage, March 27, 2008
- Heparin is now suspected in 62 fatalities across U.S.
  New York Times, April 10, 2008
- U.S. identifies tainted heparin in 11 countries
  New York Times, April 22, 2008

Solving the Chinese heparin crisis

- Outbreak of adverse reactions associated with contaminated heparin, New England Journal of Medicine, 359: 2674-2684, 2008

- Contaminated Heparin Associated with Adverse Clinical Events and Activation of the Contact System, New England Journal of Medicine, 358: 2457-2467, 2008

- Oversulfated chondroitin sulfate is a contaminant in heparin associated with adverse clinical events, Nature Biotechnology, 26: 669-675, 2008

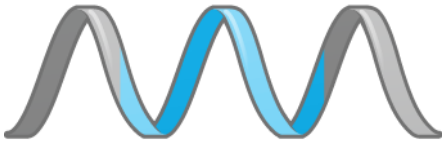


Small molecules

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

Central Dogma of Molecular Biology

DNA → messenger RNA → Protein



Hard Drive
DNA stores our genetic information

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

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

The Boston Globe

‘This is not how you do science’: Cambridge biotech Moderna’s potential COVID-19 vaccine stirs hope — and criticism

By Felice J. Freyer and Jonathan Saltzman Globe Staff, Updated May 19, 2020, 8:10 p.m.

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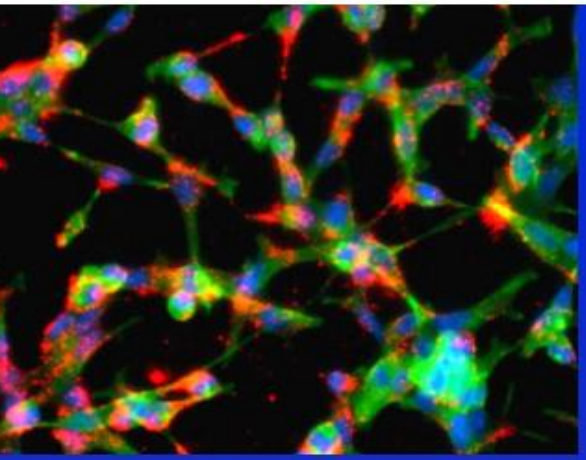
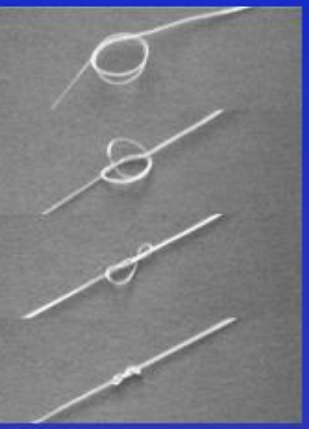
Robert S. Langer, the prolific inventor and biomedical engineering professor at MIT who cofounded Moderna, said the results of the early stage clinical trial were impressive. BARRY CHIN/GLOBE STAFF

Moderna Covid-19 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)

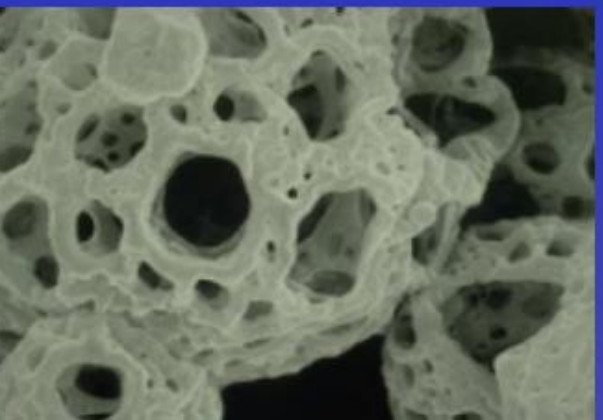

NDC 80777-273-10
Moderna
COVID-19
Vaccine
Suspension for
Intramuscular Injection
For use under
Emergency Use Authorization
Multiple-dose vial
(10 doses of 0.5 mL)

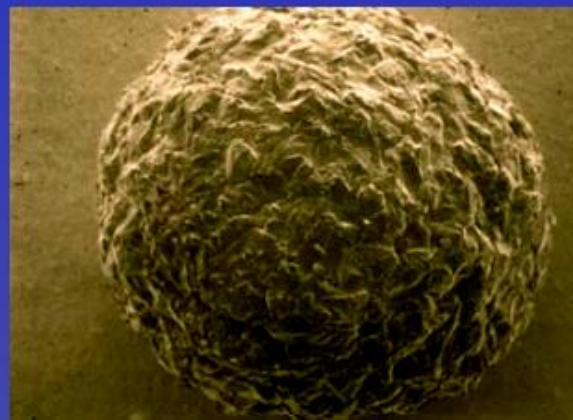




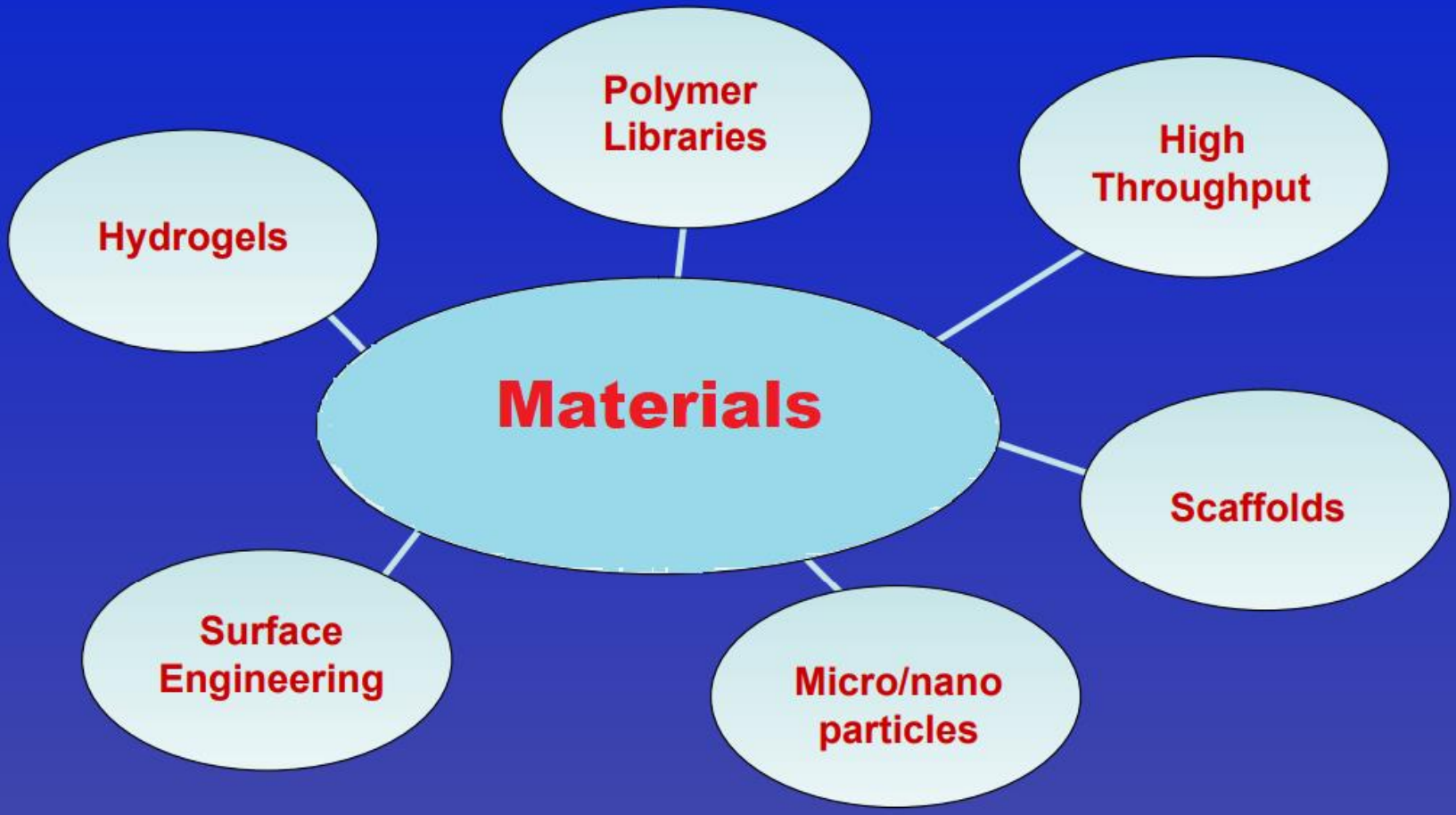
Learning from Experience: Successful Innovation at MIT

Jeffrey M. Karp





Common Link


Polymer Libraries
High Throughput
Hydrogels
Materials
Scaffolds
Surface Engineering
Micro/nano particles

"[b]eing an engineer, working in Children's Hospital was a great opportunity for me. I would see many medical problems and I started to have a lot of ideas about how to approach them. It was almost like being in a candy shop. I had a very different perspective by being an engineer. I could see how using chemistry could address this problem or engineering could address that problem. I would be riding up the elevator with clinicians and they would say, 'Well, we have trouble with this,' and I would say, 'Well, maybe we can solve this way."

Robert Langer, Interview with Peter Kolchinsky, August 18, 2000

Bob Encountered Major Difficulty To Get This Work Funded

This Approach Will Not Work Because:

- The polymer cannot be synthesized (1981)
- The polymer will react with encapsulated drug (1983)
- The polymers are fragile (1985)
- The polymer-drug system would be toxic (1986)
- The drug will not diffuse far enough to kill the remaining tumors (1988)
- Even if it does, it is a very poor drug (1990)
- The drug delivery system cannot be manufactured (1993)

So many times when you try to do something in science, when you try to invent something, people tell you that it's impossible, that it will never work. But I think that is very rarely true. I think if you really believe in yourself, if you really stick to things, there is very little that is really impossible."

Robert Langer, Interview after winning the Lemelson award, April 1998

LANGER LAB TEAM

Philosphy:
Make a difference in the world through working on significant problems that face humanity

- Academia
  - >17,300,000 USD in funding per year
  - >1,500 publications in refereed journals
  - >220 major awards
- Industry
  - >908 patents (>500 Patent Applications pending)
  - >400 licensed technologies
  - >40 spin out companies

A Multidisciplinary Lab

>100 members

Over 5,000 applications per year

- Chemists
- Chemical Engineers
- Mechanical and Electrical Engineers
- Biologists
- Biochemists
- Microbiologists
- MDs (ophthalmologists, surgeons, anesthesiologists)
- Veterinarians
- Materials Scientists

Innovation is part of the Langer Lab DNA

- **Purpose:** High risk research themes that can impact society
- **People:** Selected for intellect, passion, collaborative work, diverse expertise
- **Trust:** Researchers given intellectual space to develop their own projects while assisting other researchers
- **Respect:** Rapid feedback, critique of ideas, generous sharing of credit
- **Networking:** Internal/external collaborations; few boundaries
- **Research Model:** Idea-to-market
- **Sustained Funding:** Supports a broad rather than narrow discovery agenda

Langer's Model of an Ideal Research Project

- **A huge idea:** a critical societal need that can be met by inventing a platform product.
- **A seminal paper:** fundamental research that establishes the science underlying the product concept and its efficacy.
- **A blocking patent:** derived from patent disclosures written in parallel with the research process, and filed before publication of the research.
- **Preliminary in vivo studies:** demonstrates efficacy.

"In my own laboratory, I let people see examples of what I do. I have people running around in here all the time about 'can you patent this, can you patent that.' When people see other people do it, it increases their confidence and awareness of the way they think, and they're more likely to succeed."

Robert Langer, interview after winning the Lemelson award, April 1998

"How well does MIT's environment foster innovation…?"

"Good role models, which is one of the things the undergraduate research program provides, are very helpful…The program is a terrific way for undergraduates to learn research, and it's what makes MIT unique.

I also think that MIT goes a couple steps beyond just the education. MIT has always had strong ties to industry. There's a terrific Technology Transfer Office and Industrial Liaison program. So they have all these things that expose students and professors to a broader spectrum of things, which I think encourage innovations very well."

“It is important to encourage people to reach for their ideas, and create an environment where people can do so.”

Robert Langer, Interview with *Nature*
August 24, 2006