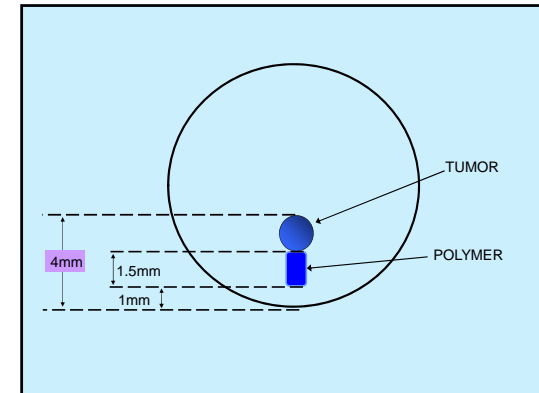
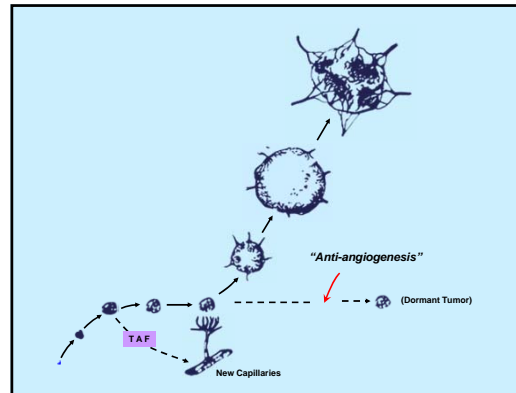


**The Edison of Medicine:
Robert Langer's quest to solve global
health challenges using biotechnology**

**Dr. Robert S. Langer, Sc.D.
Institute Professor
Massachusetts Institute of Technology**

9 October 2020 | Worcester Polytechnic Institute | University Lecture Series



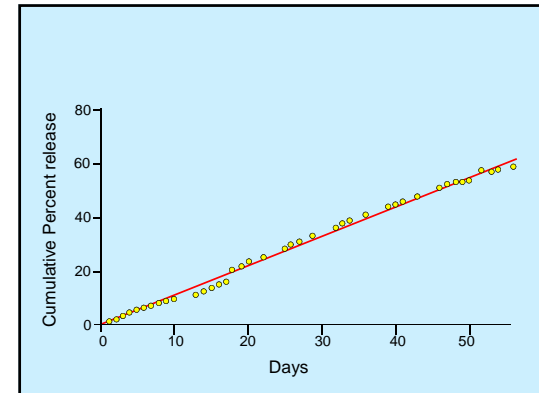
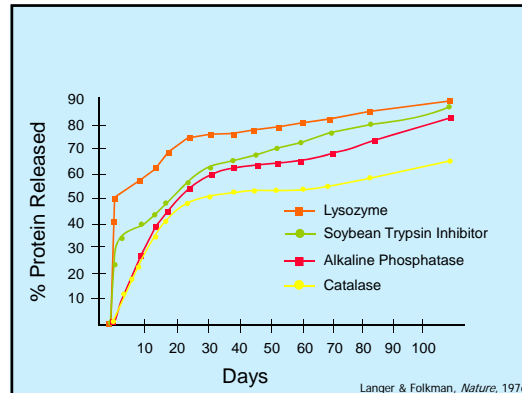
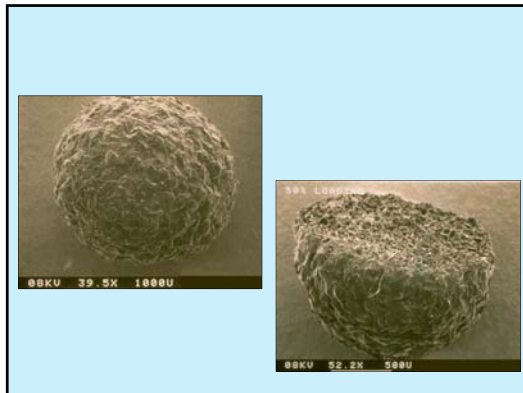
POLYPEPTIDE	Mol. Wt.	Half-Life
Growth Hormone	22,600	< 25 minutes
Insulin	6,000	< 25 minutes
Oxytocin	1,007	2 minutes
Parathyroid Hormone	9,500	< 15 minutes
Vasopressin	1,200	4 minutes

This approach will not work because

Large molecules cannot slowly diffuse through solid polymers

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

Chemical and Engineering News, 1977

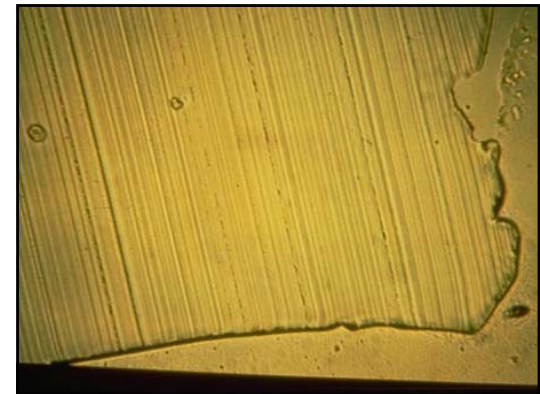


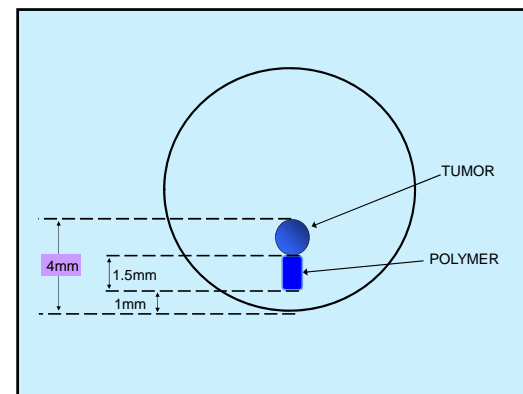
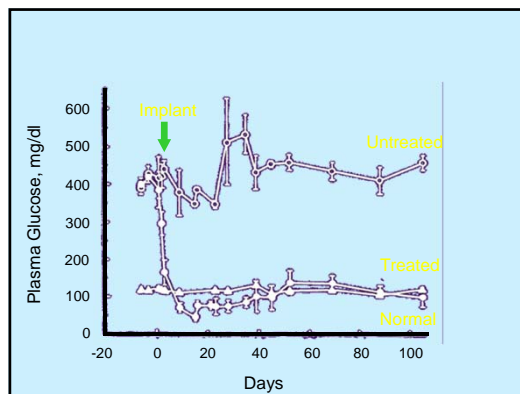
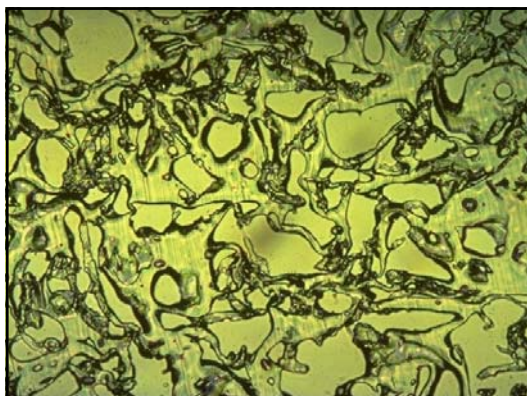
This approach will not work because

- Large molecules cannot slowly diffuse through solid polymers
- Organic solvents will denature peptides or proteins

“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 polymeric drug delivery, he blew a cloud of smoke in Langer’s face and said, ‘You better start looking for another job.’ I thought I was in a Fellini movie.”

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

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	Toriseal (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

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

- Two phase system
- 1st phase – polymer with water sorptivity not greater than 50%
- 2nd phase – agglomerated macro-molecular material of MW at least 1000

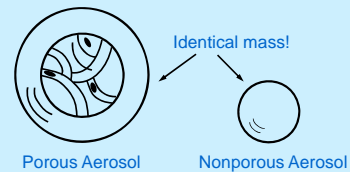


Enzytech/Alkermes

- > 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

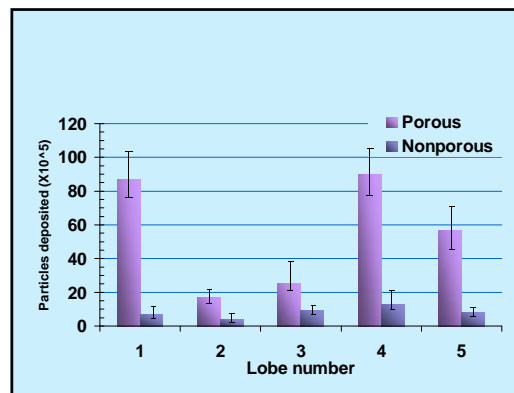
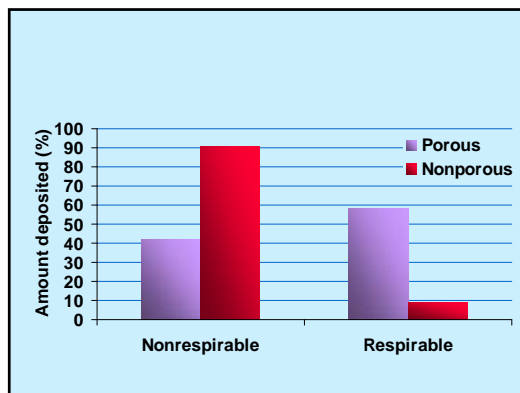
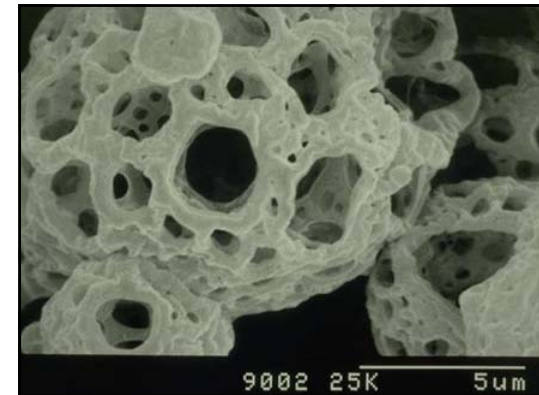
Advantages of porous aerosols for inhalation therapy

Optimal size for deep lung deposition

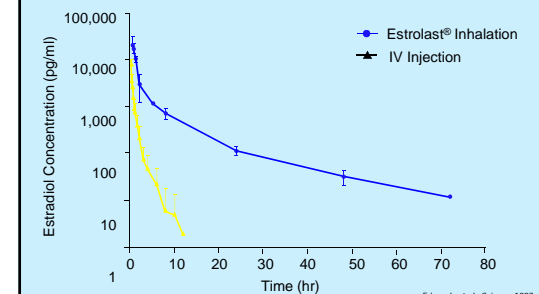


Advantages of large size for therapeutic aerosols

- > Easier aerosolization and flowability
- > Less prone to phagocytosis



Pharmacokinetic profile of estrolast

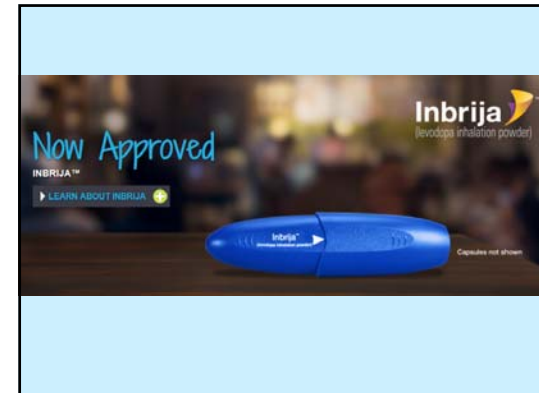


U.S. Patent 5,874,064: Edwards, Langer, Lotan et al

- > A particulate system for drug delivery to the pulmonary system
 - ◆ Particles have a density less than 0.4 g/cm³
 - ◆ Particles have a mean diameter between 5 and 30 μm
 - ◆ Agent is incorporated into or adsorbed into particles

A brief history of AIR

1996	Initial studies
1997	<i>Science</i> publication
1998	AIR in Cambridge
1998	Deals with Lilly, Glaxo, Pfizer; 2 clinical trials
1999	Merger (>1000% IRR for investors)
2000s	Edwards spins off MEND – new treatments for this technology, Alkermes spins off Civitas; Civitas acquired by Acorda for \$525M



Biomolecules

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

Our Discoveries

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
- 2011 Major investment by Baxter
- 2016 Major investment by Mylan
- 2017 Major Investment by CSL
- 2018 1st Lovenox biogeneric approved by FDA 7/23/201 (1st complex drug approved based on analytic data; largest syringe launch in history). Copaxone approved by FDA 2015.
- 2020 Johnson & Johnson acquires Momenta for \$6.5 billion dollars



Momenta Pharma soars on landmark FDA approval

July 23, 2010

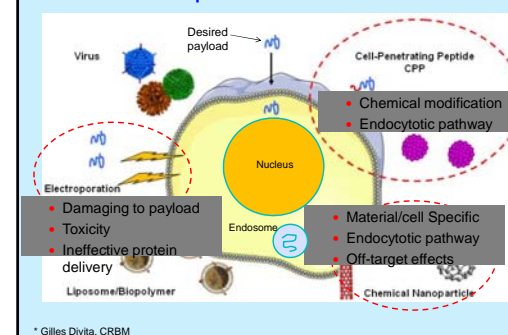
Heparin crisis

- 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

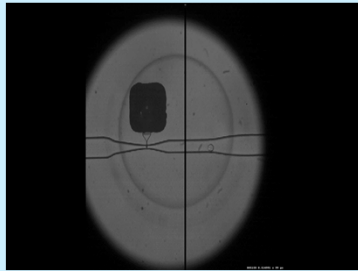
Solving the Chinese heparin crisis

- 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

Current techniques



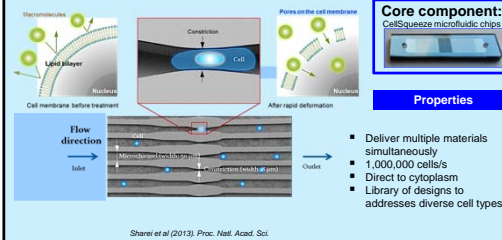
Rapid mechanical deformation



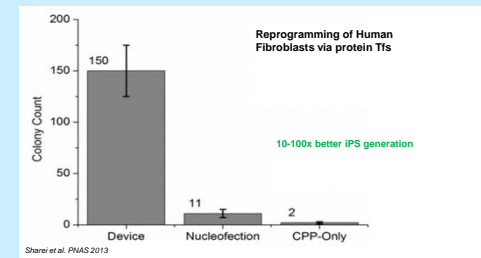
Treatment rate~1,000,000 cells/s

A. Sharei, et al. PNAS 2013

Technology: CellSqueeze

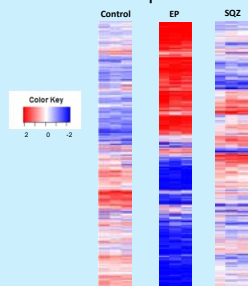


Demonstrated efficacy in previously challenging applications



Dramatic functional advantages relative to EP

Full transcriptome microarray



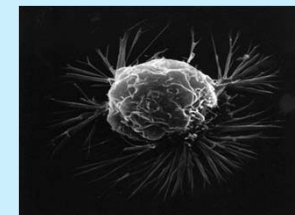
Top ten world-changing ideas

World Changing Ideas 2014



1. CRISPR/Cas9: The gene genie
2. SQZ Biotech: Reprogrammable cells
3. Transparent organisms
4. Spit-fired fuel cells
5. Vision-correcting displays
6. Atomic-scale legos
7. Ultrahard recyclable plastics
8. Wireless charging with sound waves
9. Batteries that capture low-grade waste heat
10. Video cameras for nanoparticles

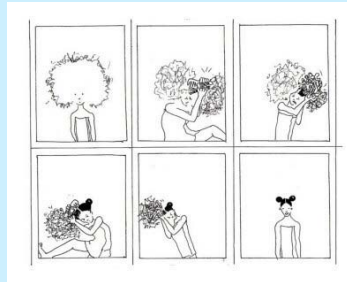
“SQZ Biotech signs up to \$1B immuno-oncology deal with Roche”



17 October 2018, Pharmaceutical-Technology.com

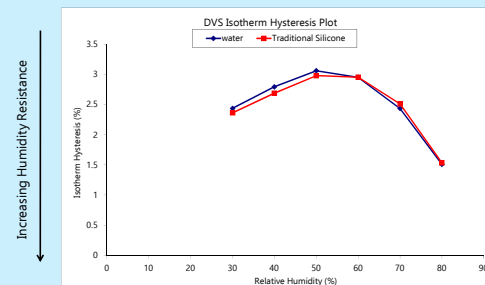
frizz

Living Proof thought there had to be another way

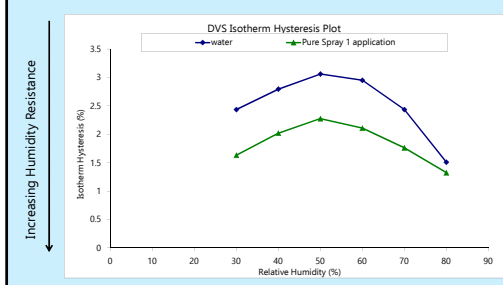


The problem – Humidity

Silicones don't fight humidity



No Frizz blocks out humidity



No Frizz shampoo and conditioners



Deposits PolyfluoroEster to effectively block humidity & reduce friction in hair resulting in hair that's soft, smooth and shiny

Improves the performance of No Frizz styling products

Shampoo features an exclusive sulfate-free surfactant system and provides extra gentle cleansing

Conditioner weightlessly hydrates without oils or silicones



Jennifer Aniston
named
spokesmodel and
investor of Living
Proof hair care

OTRC
10/11/12

Companies

- 1987 Enzytech—Microsphere drug delivery (merged with Alkermes)
- 1987 Opta Foods—Food ingredients (originally part of Enzytech, acquired by Sun Foods)
- 1988 Neomorphics—Biocompatible materials for tissue growth (acquired by Advanced Tissue Sciences and Smith & Nephew)
- 1992 Focal—Biodegradable materials for prevention of surgical adhesion (acquired by Genzyme)
- 1993 Acusphere—Imaging agents with porous microsphere technology
- 1993 EnzyMed—Combinatorial pharmaceuticals (acquired by Albany Molecular Research)
- 1997 Advanced Inhalation Research—Pulmonary drug delivery (acquired by Alkermes)(Civitas acquired by Acorda)
- 1998 Reprogenesis—Scaffolds for tissue growth (merged with Creative Biomolecules and Ontogeny to form Curis)
- 1998 Sontra Medical—Transdermal drug delivery (acquired Echo Therapeutics)
- 1999 Transform Pharmaceuticals—Polymorph crystallization (acquired by Johnson & Johnson)
- 1999 MicroCHIPS—Silicon-chip-based drug delivery

Companies

2000	Combinent Biomedical Systems—Transvaginal drug delivery (acquired by Juniper)
2001	Momenta Pharmaceuticals—Complex-sugar-based therapeutics
2003	Pulmatrix—Inhaled therapeutics
2004	Pervasis—Therapeutics for vascular healing (acquired by Shire)
2005	Living Proof—Hair care products (acquired by Unilever)
2005	Arsenal Medical—Bioresorbable scaffolds
2005	PureTech Health – New ways to treat GI and immune disorders
2005	In Vivo Therapeutics—Scaffolds for spinal cord therapy
2006	T2 Biosystems—Nanoparticle-based diagnostics
2006	Semprus BioSciences—Medical device coatings (acquired by Teleflex)
2006	BIND Biosciences—Targeted nanoparticle-based therapeutics (acquired by Pfizer)
2007	Selecta Biosciences—Targeted nanoparticles
2008	Seventh Sense Biosystems—Microneedle blood collection technology
2008	Taris BioMedical—Urological drug delivery (acquired by Johnson and Johnson)
2009	Kala Pharmaceuticals—Mucosal drug delivery
2011	ModeRNA—Modified messenger RNA delivery

Companies

2011	Tarveda (Formerly "Blend Therapeutics")—Combination medicines
2013	SQZ – Delivery to cells
2013	Tissium (Formerly Gecko Biomedical) – Medical adhesives
2014	Arsia – Antibody formulations (acquired by Eagle Pharmaceuticals)
2015	Lyndra – Super long acting oral delivery
2015	Frequency Therapeutics – Molecules to restore hearing and other tissues
2015	Olivo Labs – Novel skin care (acquired by Shiseido)
2016	Sigilon– Super biocompatible materials/cell encapsulation
2017	Suono Bio – Gastrointestinal delivery
2018	Vivtex—Oral drug development
2019	Lyra Pharmaceuticals (Spun off Arsenal Medical)