Yesterday, today and tomorrow

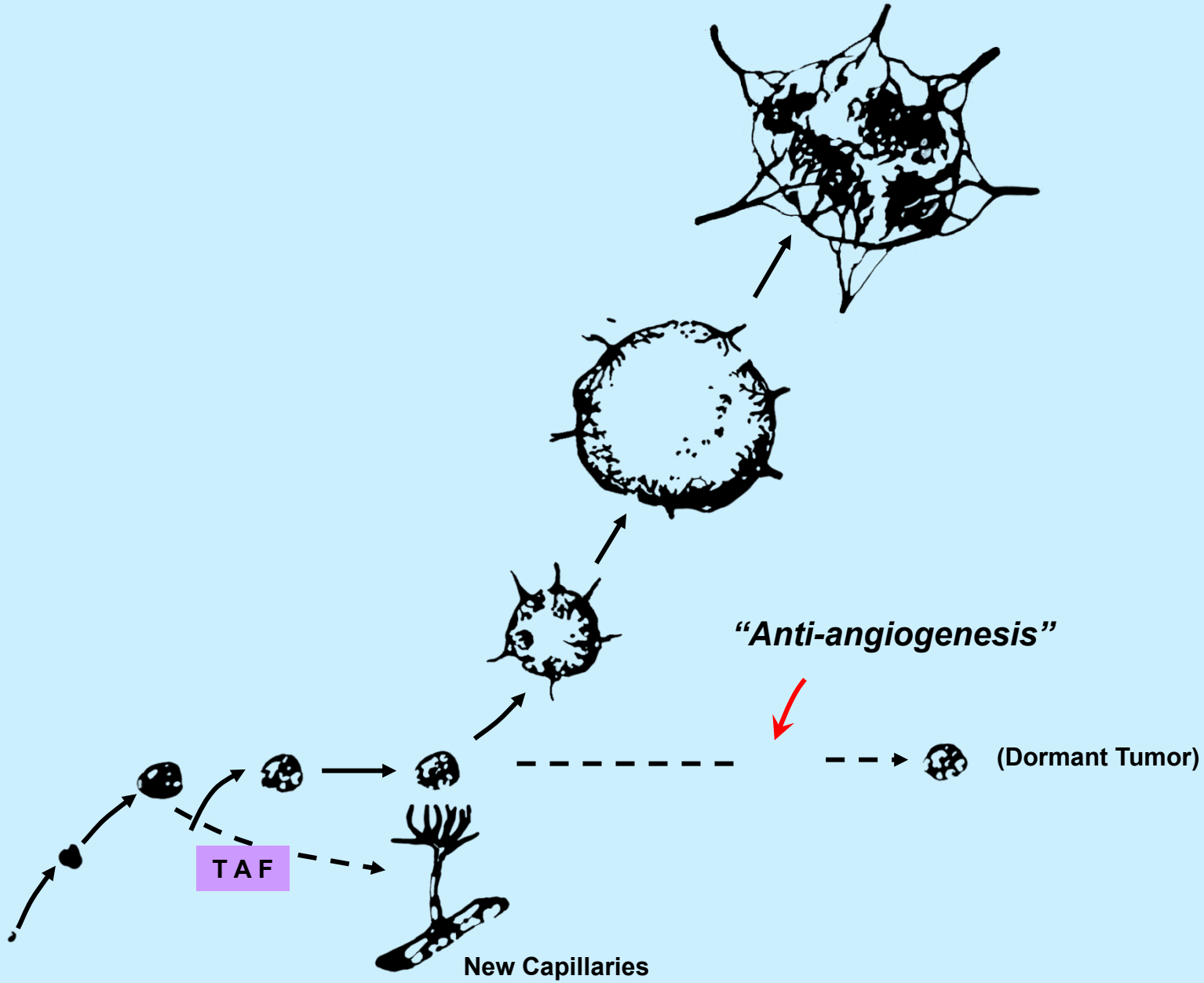
Section 3—Engineering in Drug Development and Therapeutics

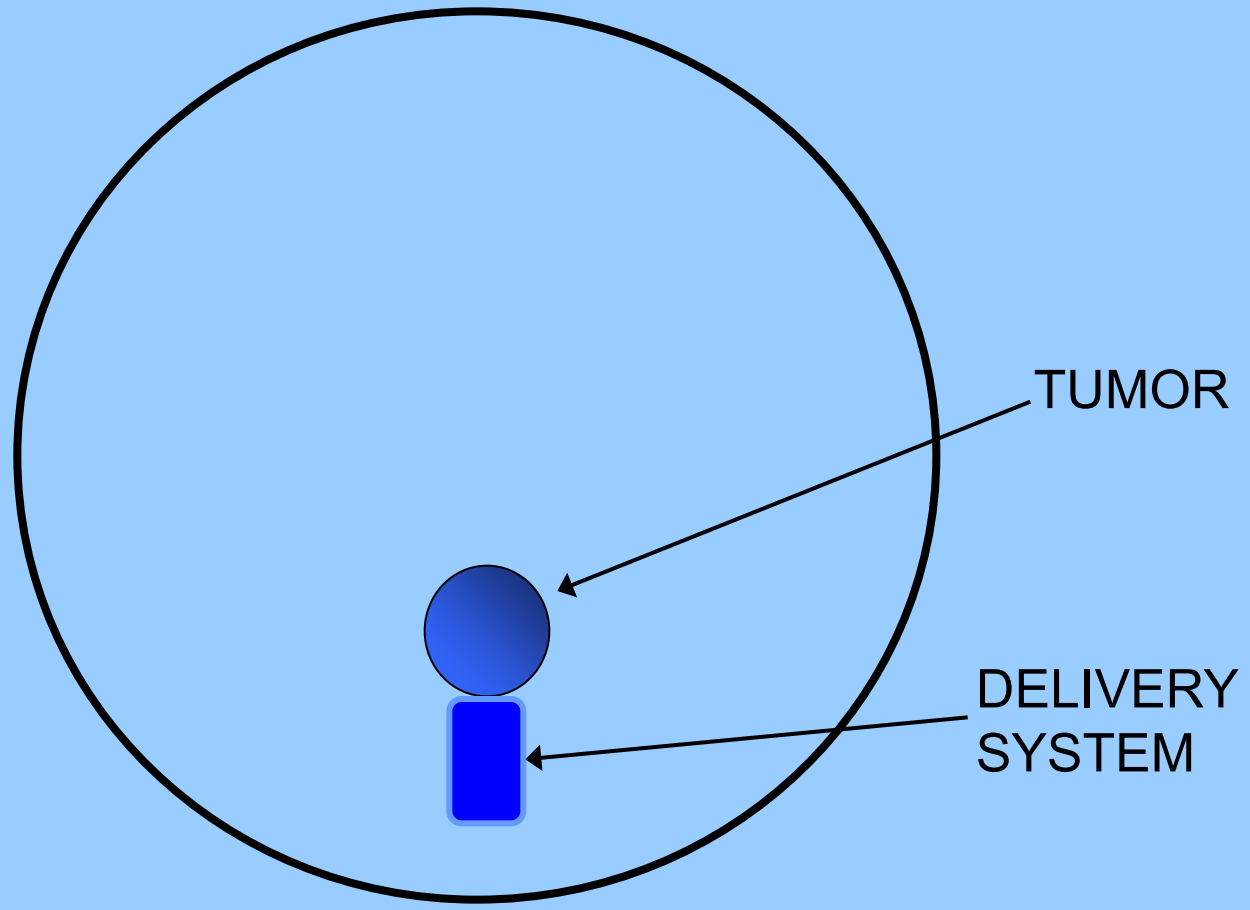
20 May 2025
National Cancer Policy Forum

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

Disclosure of potential competing interests

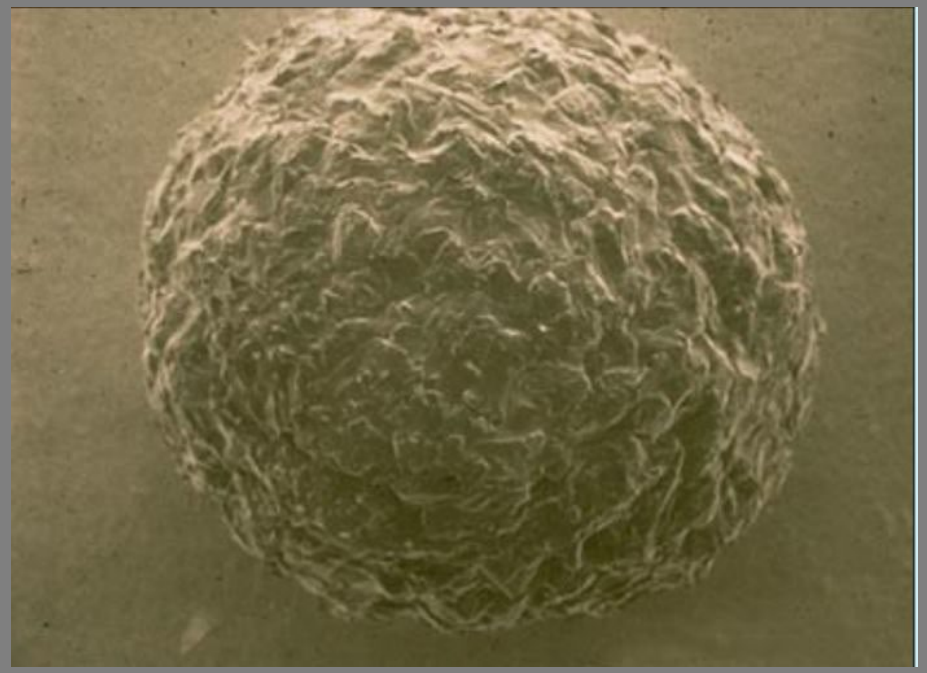
- Alnylam
- Combined Therapeutics
- Moderna

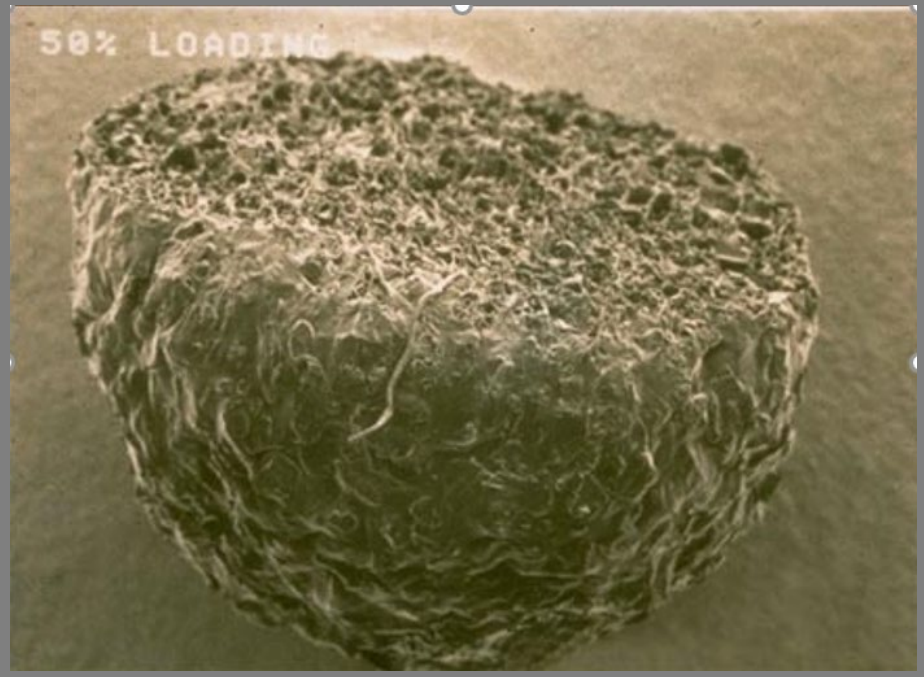

"Anti-angiogenesis"
(Dormant Tumor)
TAF
New Capillaries

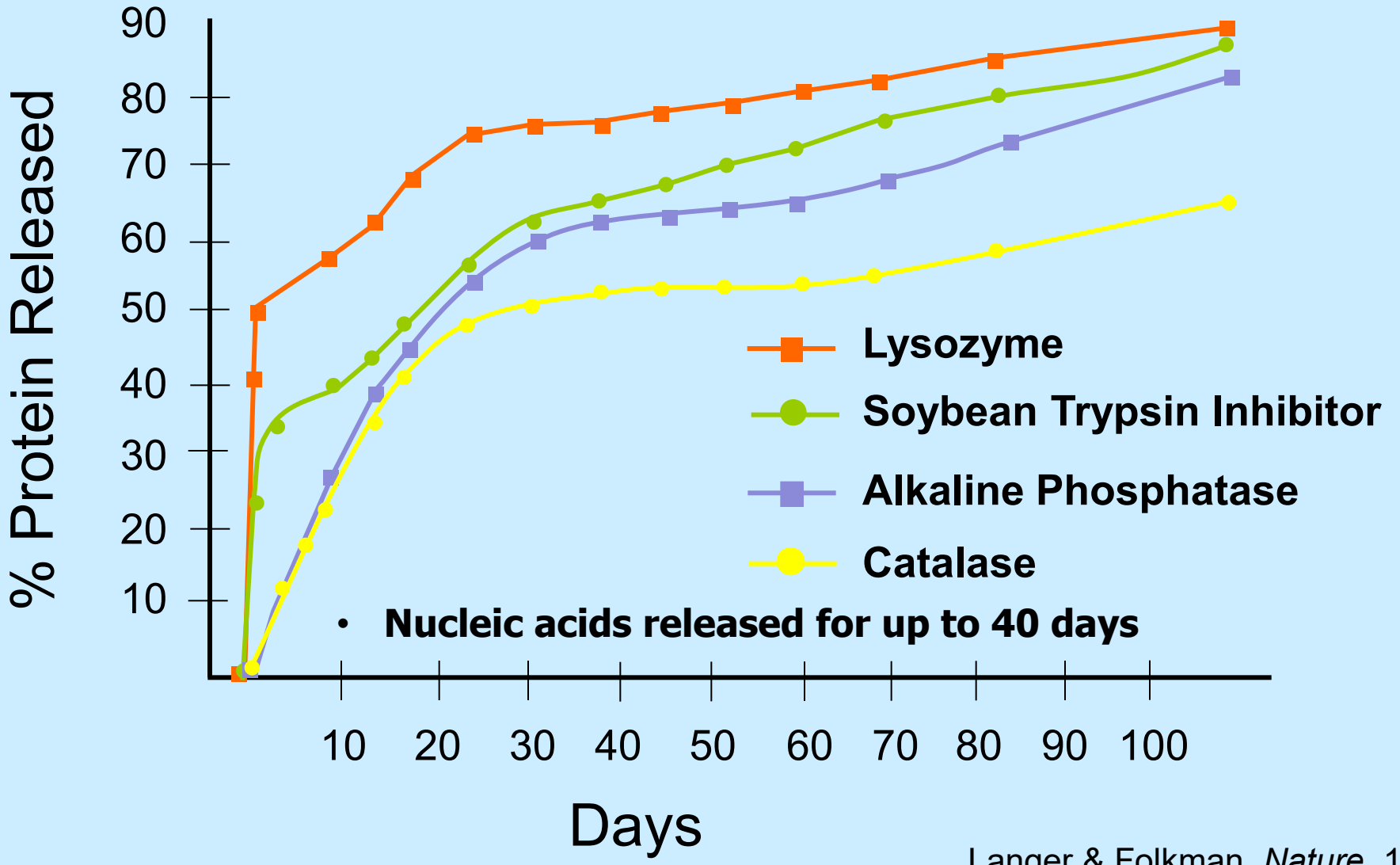

TUMOR
DELIVERY
SYSTEM

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

Large molecules cannot slowly pass through solid materials

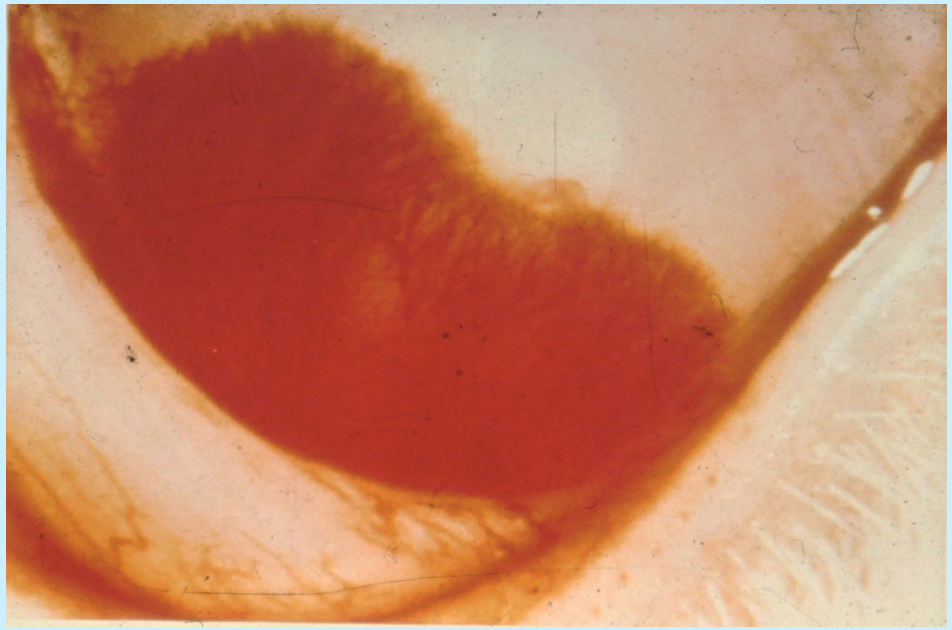



50% LOADING

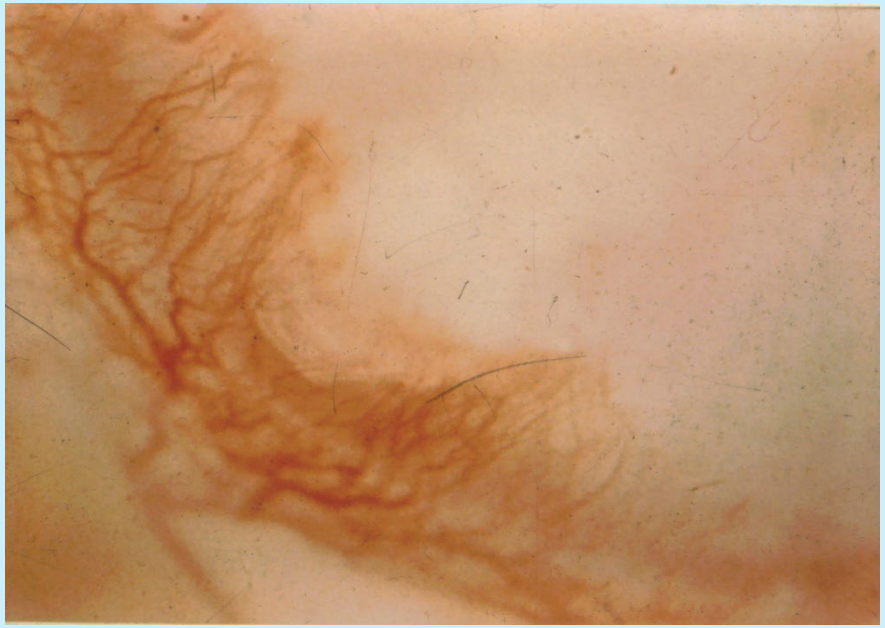


Langer & Folkman, *Nature*, 1976

Rabbit corneal pocket assay



-CDI

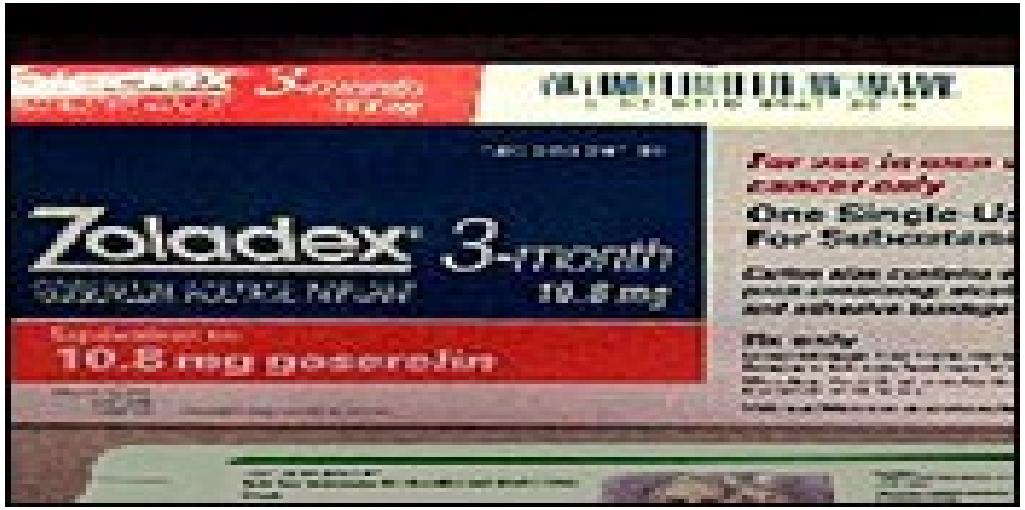


+CDI

Langer et al, *Science*, 1976

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


Zoladex 3-month
10.8 mg
10.8 mg goserelin


LUPRON
DEPOT


NDC 0075-9995-08
GLIADEL Wafer
(polifeprosan 20 with carmustine implant)
7.7 mg carmustine/wafer
Each sterile wafer contains 192.3 mg polifeprosan 20 and 7.7 mg carmustine.
Contents:
8 wafers, individually packaged
Store at or below -20°C (-4°F)
Warning: Cytotoxic agent
See package insert for full prescribing information.
Caution: Federal law prohibits dispensing without prescription.


3 mois

Today

1. ***Chemotherapy***

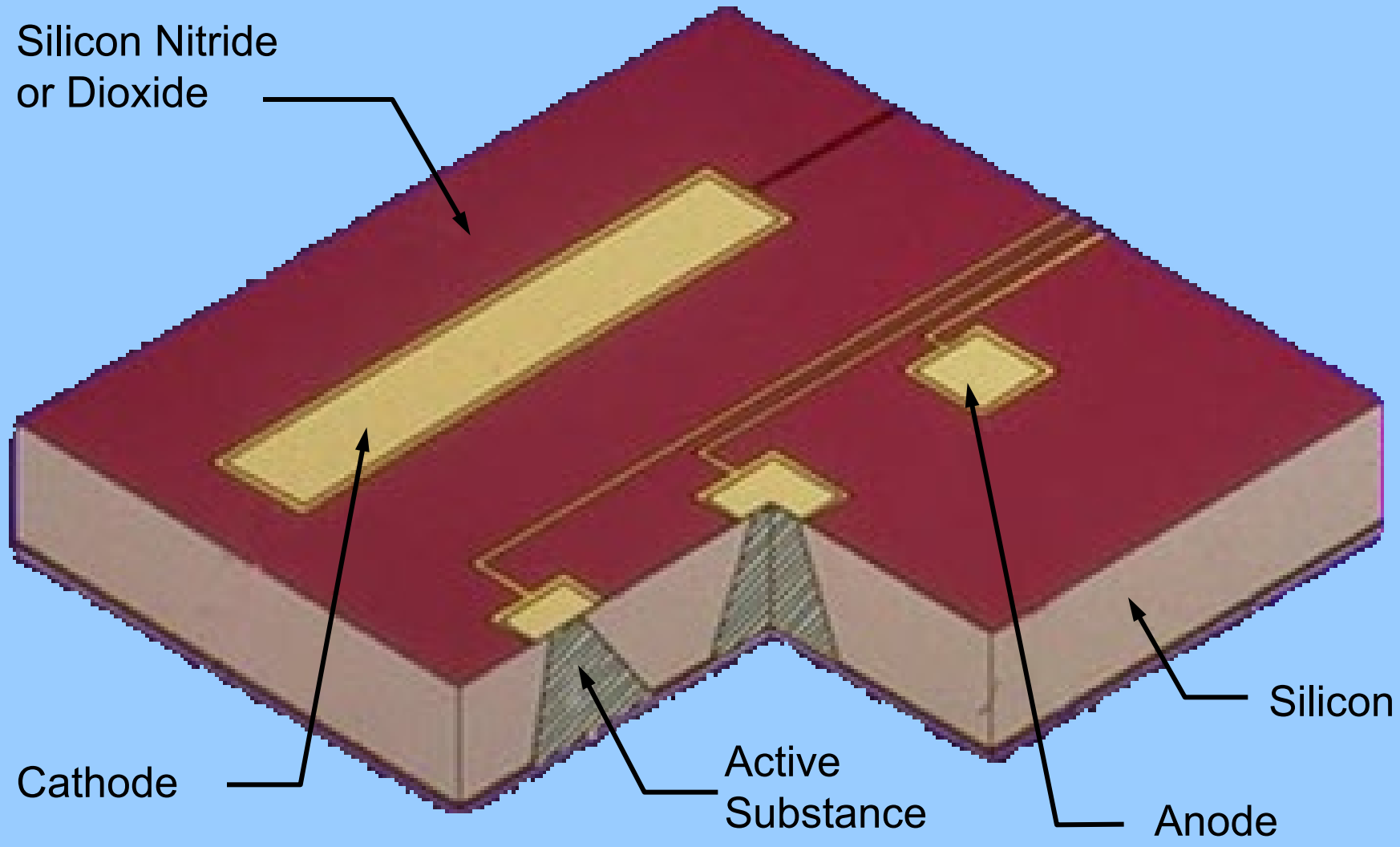
2. ***Immunotherapy***

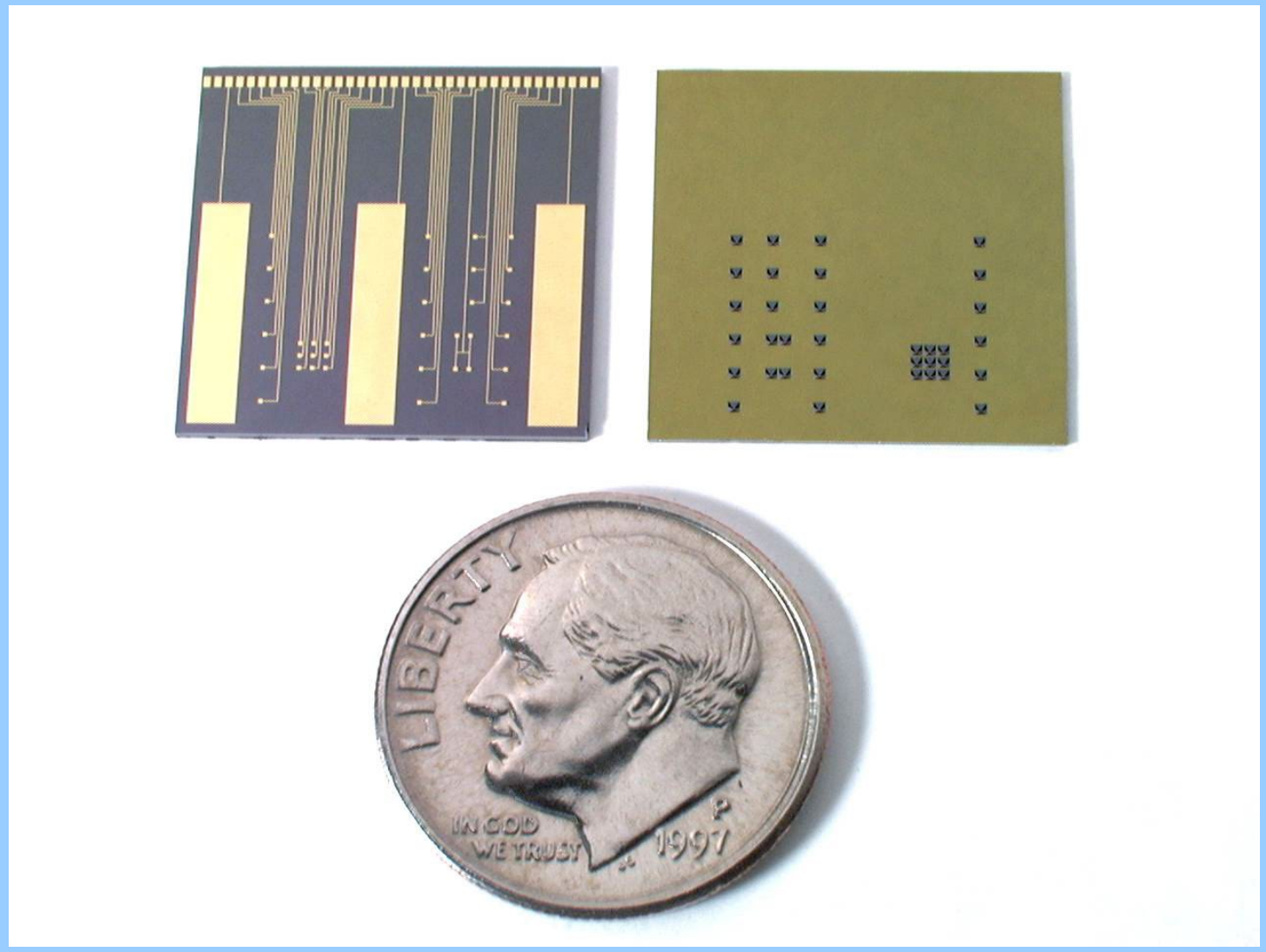
3. ***CAR T Cells***

4. ***Circulating Tumor Cells***

A controlled-release microchip, *Nature*, 397: 335-338, 1999.

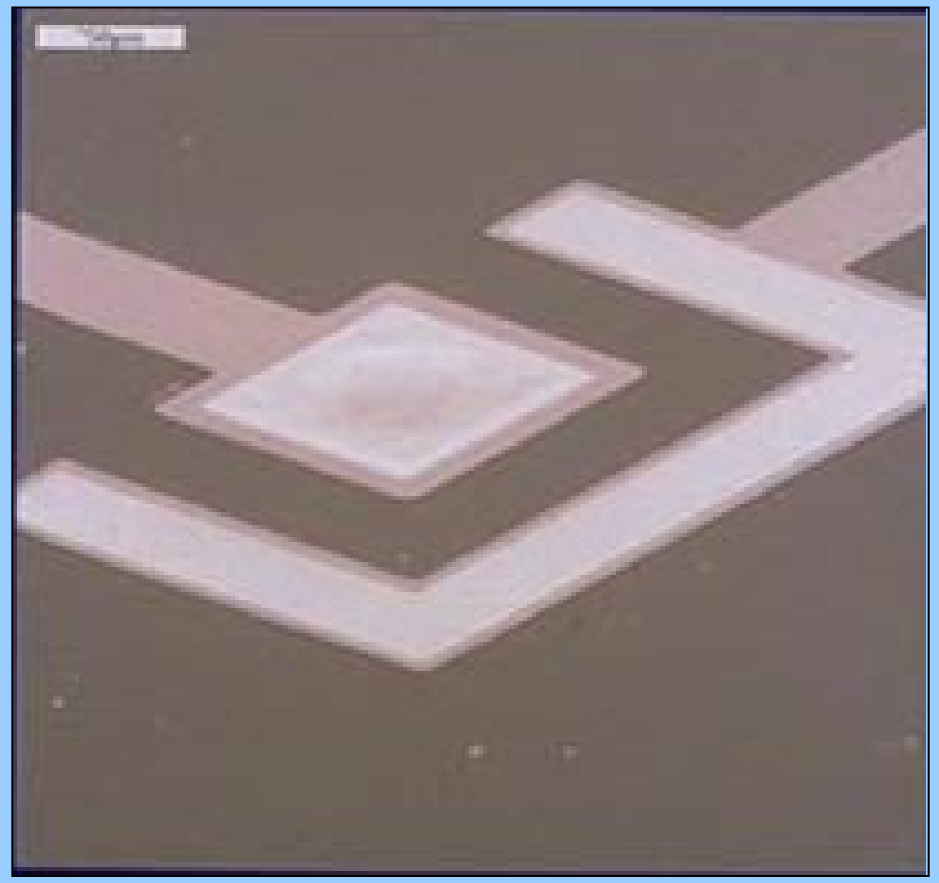
Prototype device



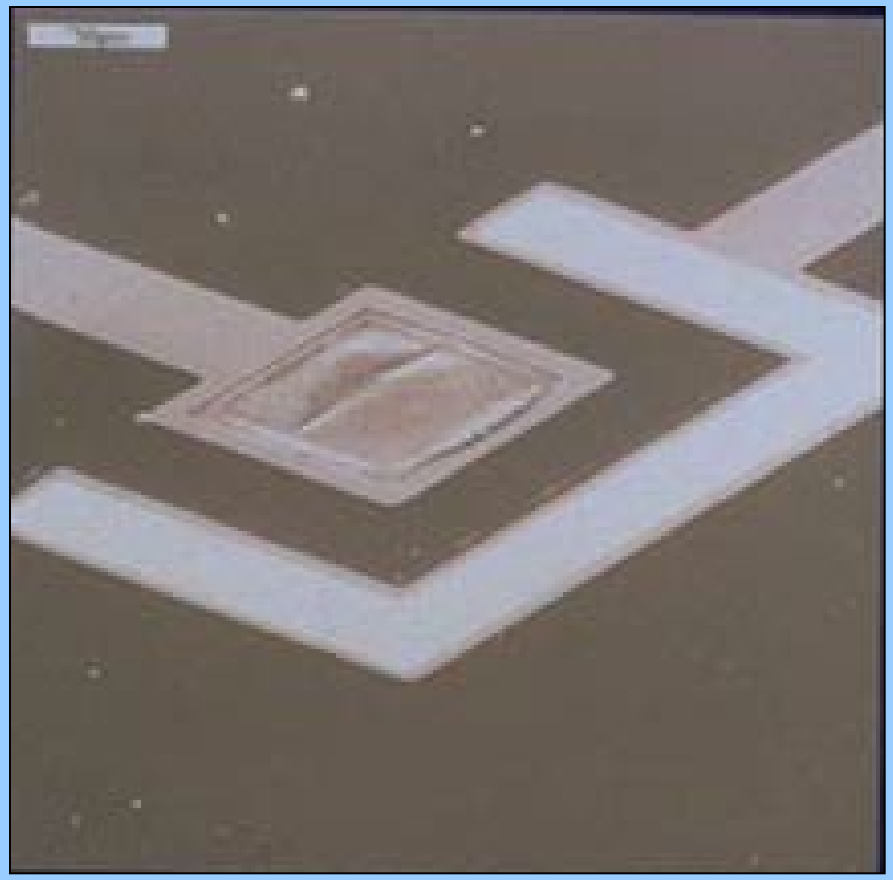

LIBERTY
IN GOD
WE TRUST
1997
P

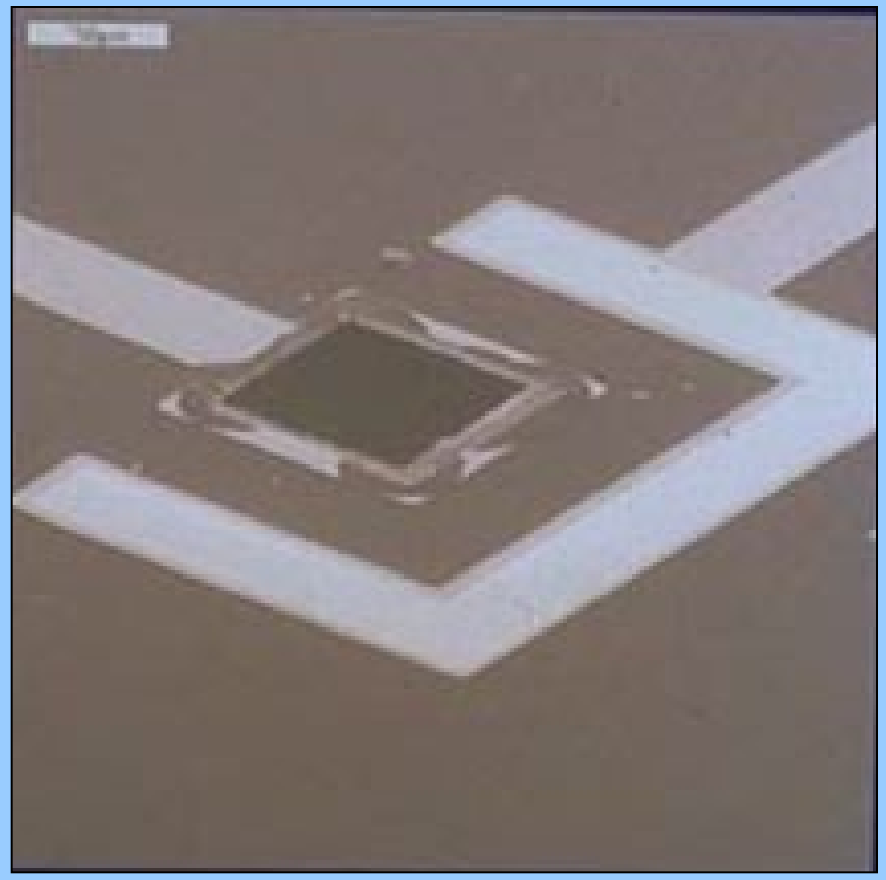
Reservoir activation

- SEM of a reservoir – electrode system before application of an electric potential



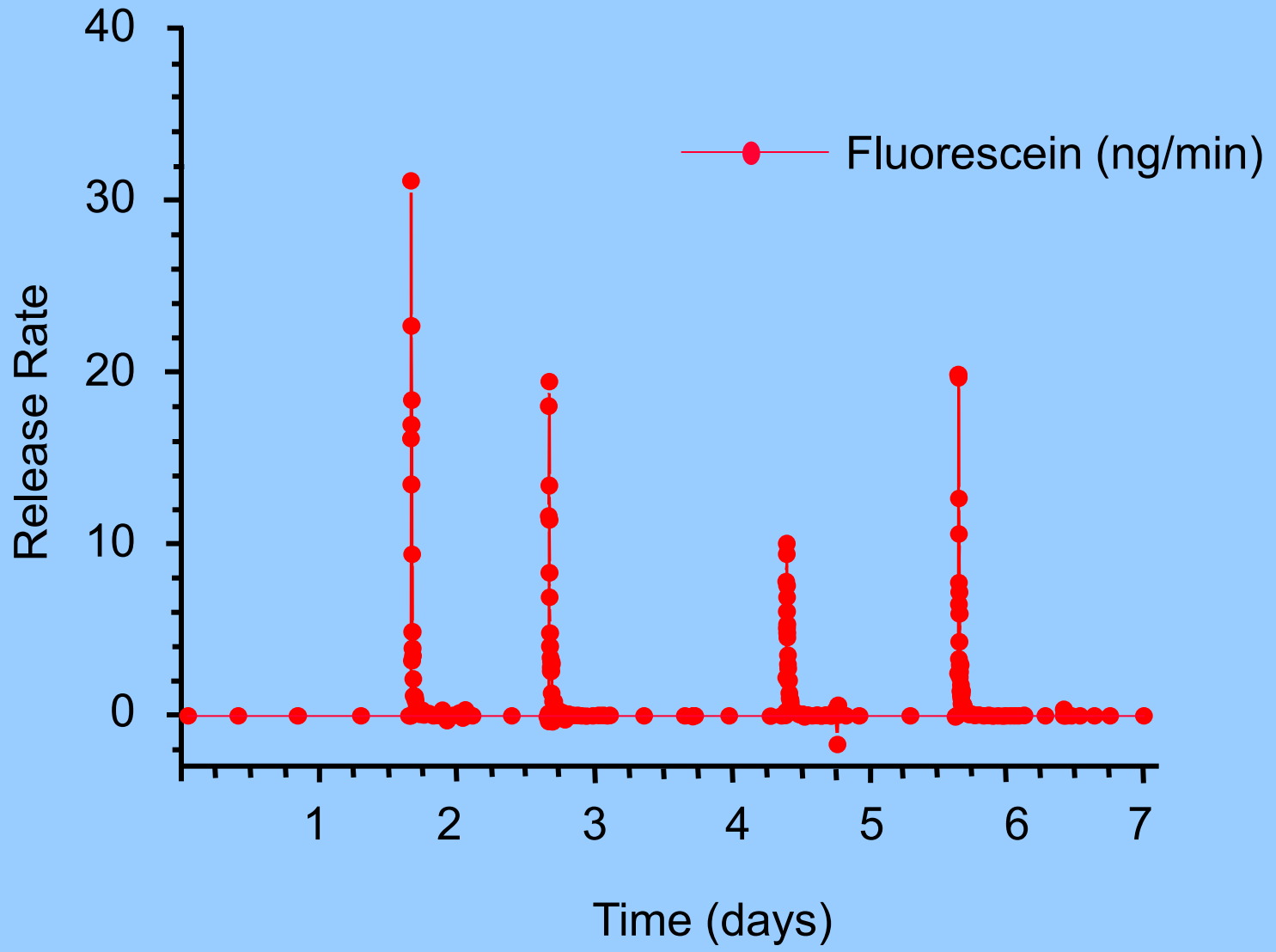
Reservoir activation



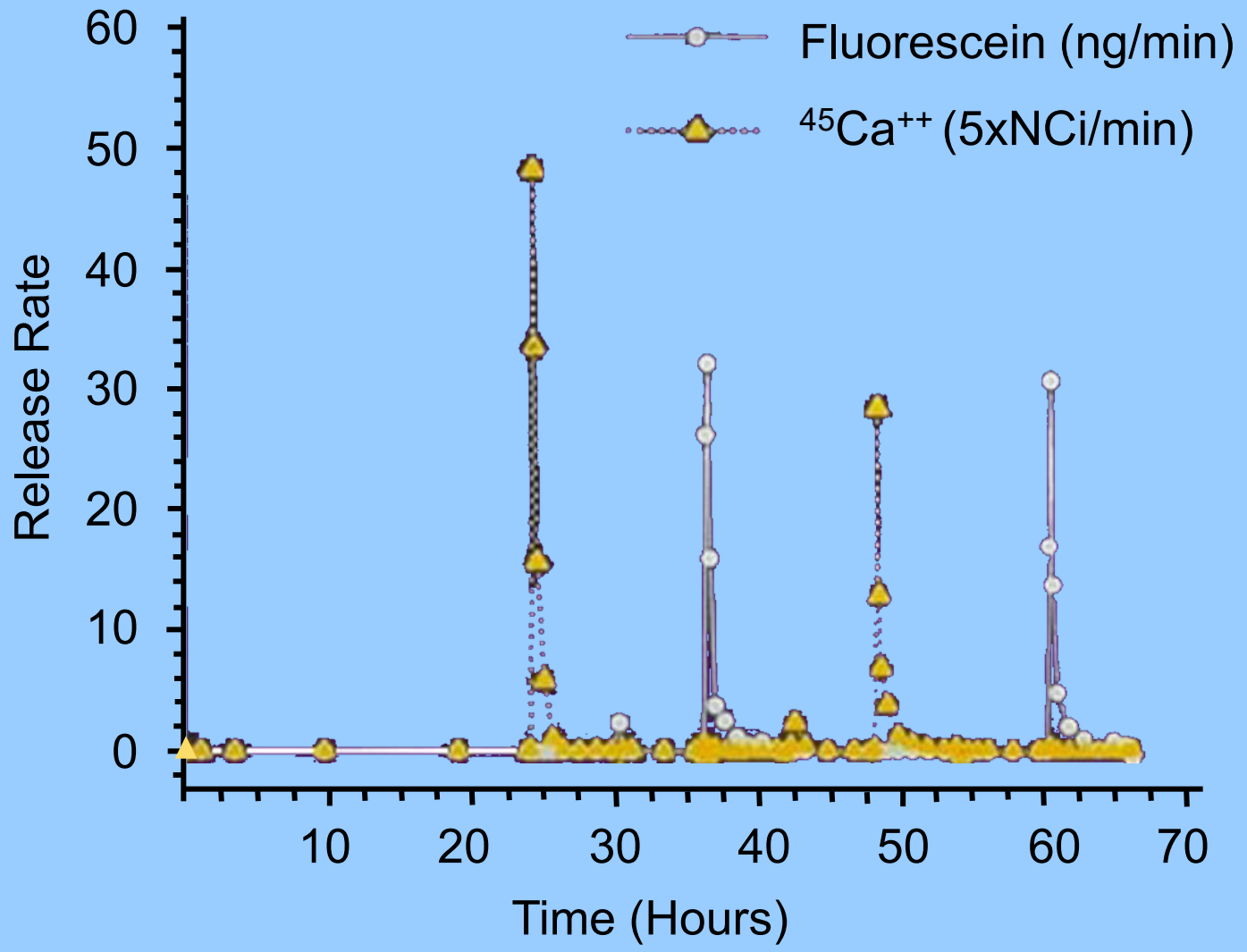


- SEMs taken after application of 1.04 volts vs. SCE in PBS

Single compound release

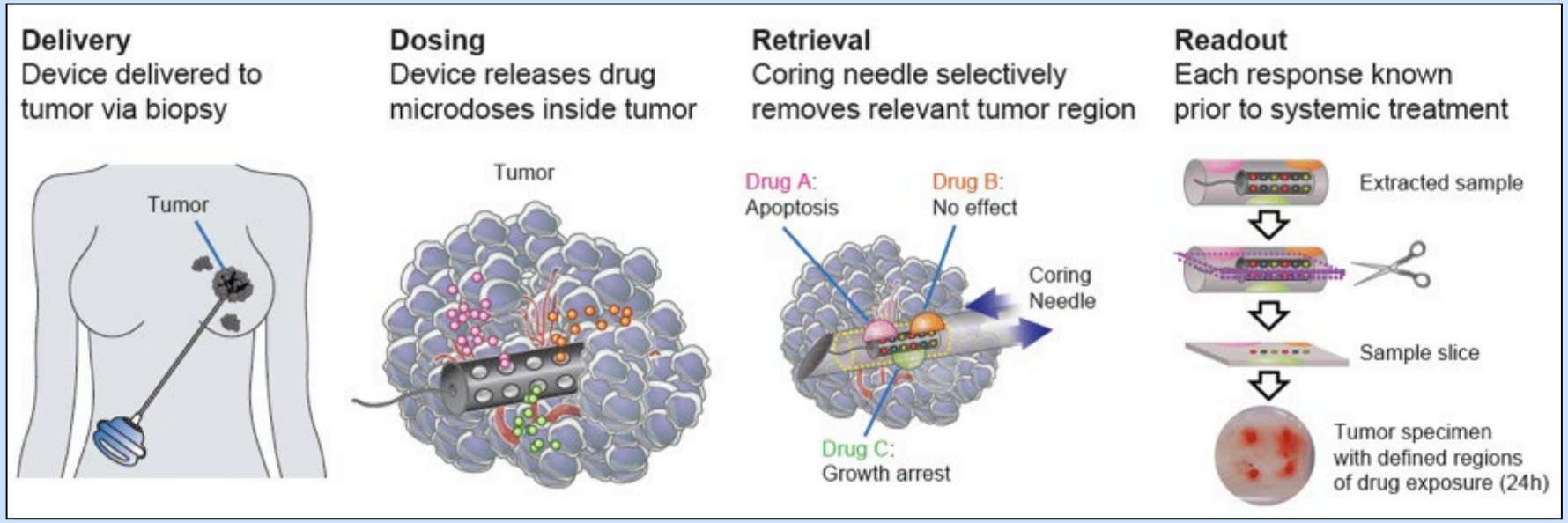


Multiple compound release



Concept

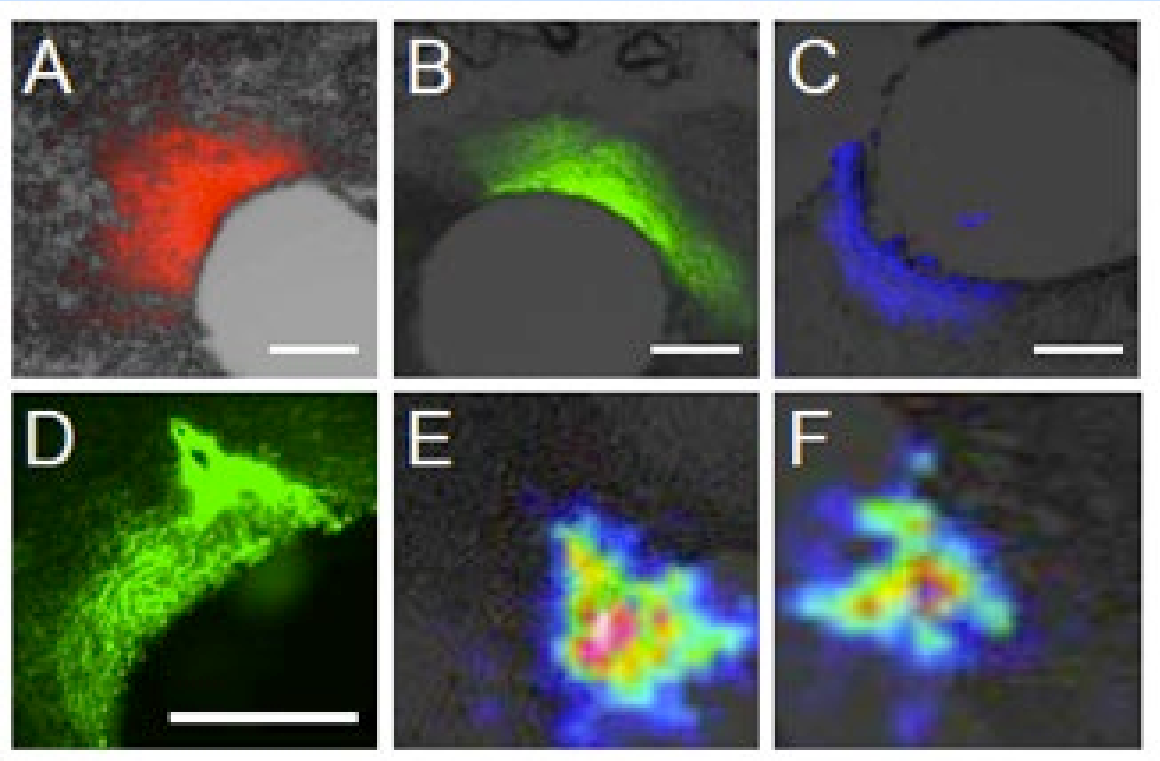
Multiple drugs or rational combinations of drugs are empirically tested *in vivo* in each person's tumor, enabling the best treatment decisions by the oncologist



Actual device

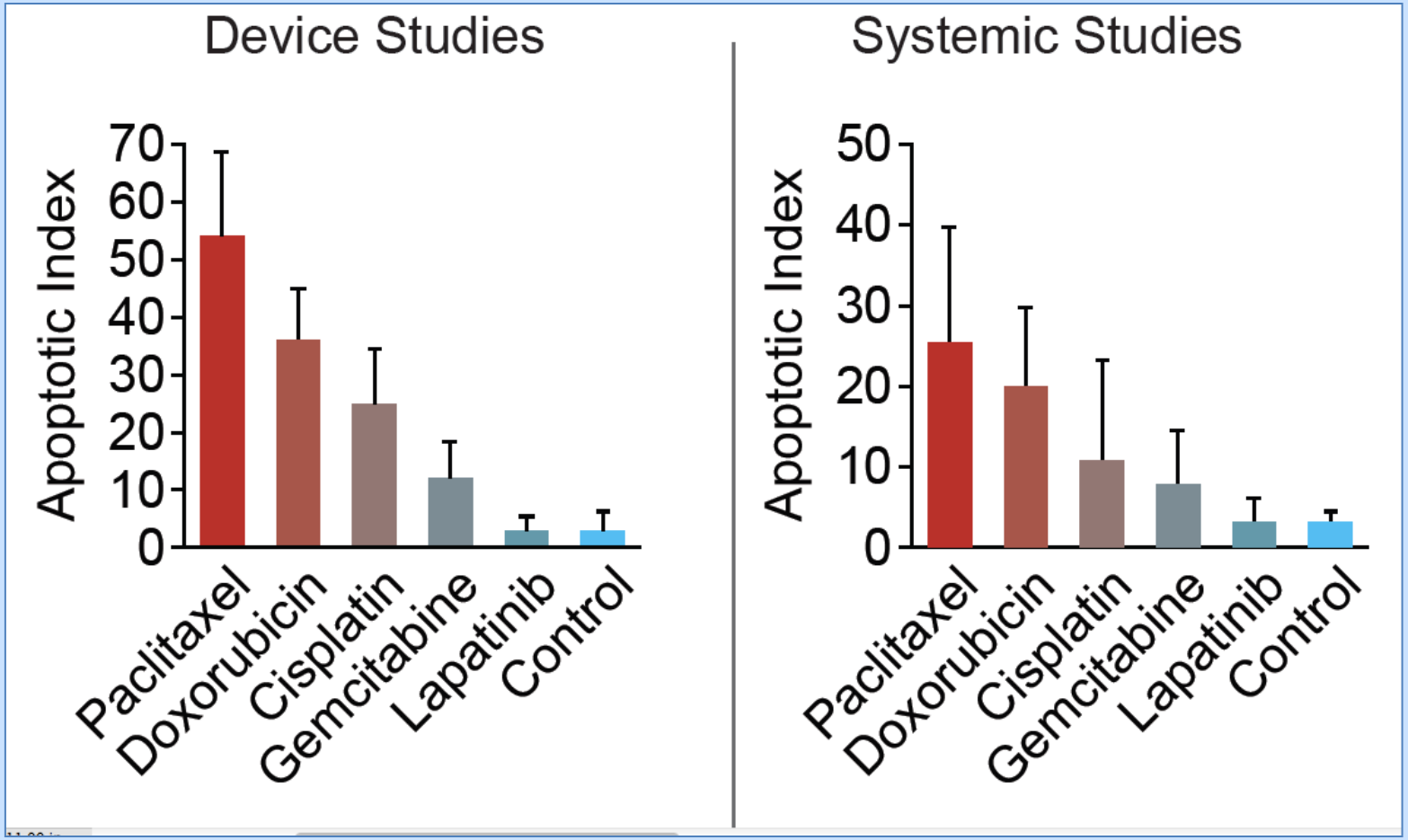
- Test phenotypic response to drug inside the native tumor microenvironment
- For 30 or more drugs or combinations in parallel
- Within 1-2 days
- Minimally invasive
- No systemic exposure to any drugs
  - One millionth of systemic dose of each drug

Deliver multiple drugs to confined regions of tumor



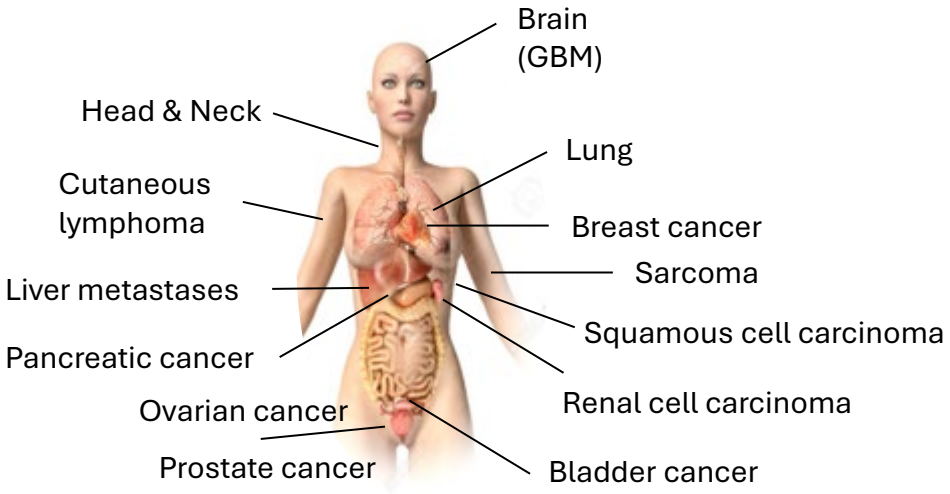
Anti-cancer drugs are delivered into confined regions of tumor. Detection by fluorescence: (A) Doxorubicin (B) Sunitinib (C) Lapatinib. (D) Cetuximab conjugated with Alexa488. Detection by MALDI mass spectrometry: (E) Gemcitabine and (F) Docetaxel.

Efficacy of five drugs in a patient derived TNBC tumor model



Description of the IMD clinical platform : active programs

13 FDA-Approved Clinical Programs Across a Diversity of Cancer Indications



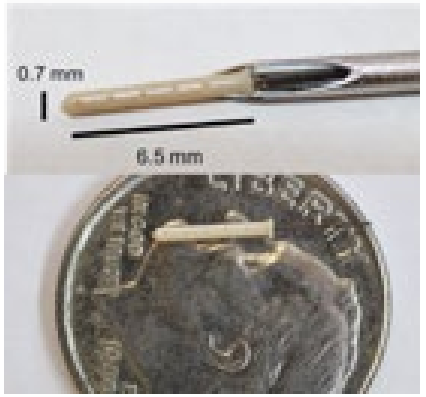
Clinical & regulatory paradigm

- 13 Active INDs are continually enrolling patients
- Framework in place with FDA to add novel/unapproved agents quickly to active protocols through amendments

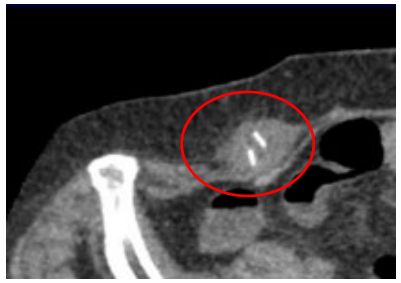
Extensive Human Safety & Feasibility record

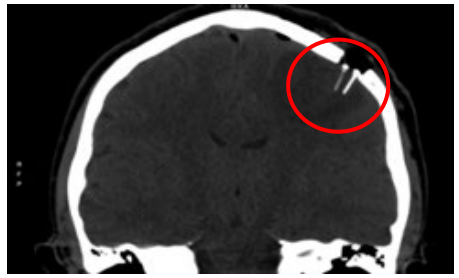
- ~300 microdevices implanted in 100+ patients
- Excellent safety & feasibility profile
- 100+ therapies tested: Small molecule, Antibody, ADCs, Cytokines, Combinations

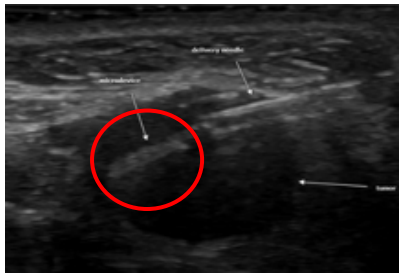
Microdevice: Clinical implementation

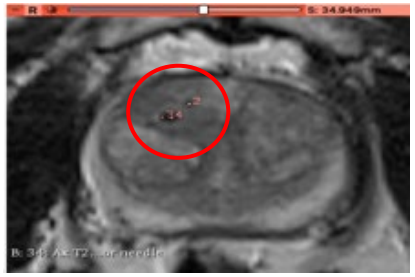


- 300 Microdevices have been placed into multiple organs (including breast, lung, brain, bladder, ovarian, prostate, T-cell lymphoma, Head & Neck, kidney); additional trials pending
- Microdevices are delivered by 19g biopsy needle. We typically place 3-6 microdevices per patient.
- Success rate of placement in ongoing trials >99%. Procedure is highly similar to fiducial or seed placements.
- Tumor-device specimen retrieval at surgery or minimally invasive


Ovarian tumor (CT)


Glioblastoma (MRI, CT)


Head and neck tumor (Ultrasound)


Prostate tumor (MRI)

Placement and visibility:
Devices are made from PEKK radiopaque polymer with visibility on CT, MRI, ultrasound, or x-ray/fluoro


ANNALS OF SURGERY

First-in-Human Intrathoracic Implantation of Multidrug-Eluting Microdevices for In Situ Chemotherapeutic Sensitivity Testing as Proof of Concept in Nonsmall Cell Lung Cancer


THE JOURNAL OF UROLOGY

Original Clinical Article

Novel Intraprostatic MR-Guided Implantation of Multidrug-Eluting Microdevice for Testing of Systemic Therapy Agents In Situ: Proof of Concept in Intermediate-Risk and High-Risk Prostate Cancer


SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

Intratumoral drug-releasing microdevices allow in situ high-throughput pharmaco phenotyping in patients with gliomas

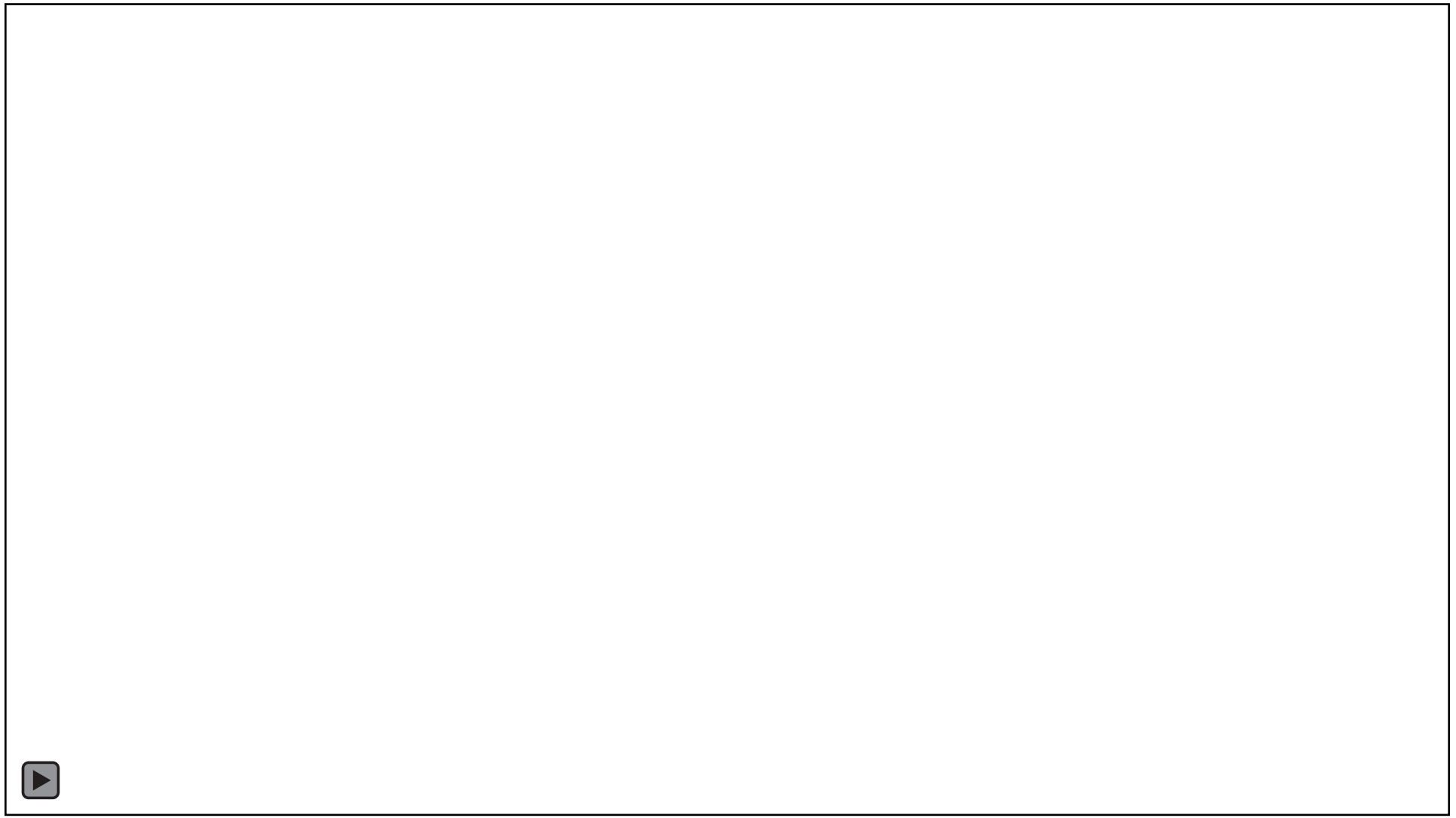
Regulatory

- GMP manufacturing
- Full quality system
- Master Access File with FDA

- Approved agents (on or off-label)
- Unapproved agents in clinical testing (requiring only cross-reference letter)
- Novel agents (requiring minimal toxicology testing).

- Small molecule cytotoxic and targeted agents
- Immune-modulating agents, including checkpoint inhibitors and cytokines
- Antibody-drug conjugates
- Combinations of up to 4 agents

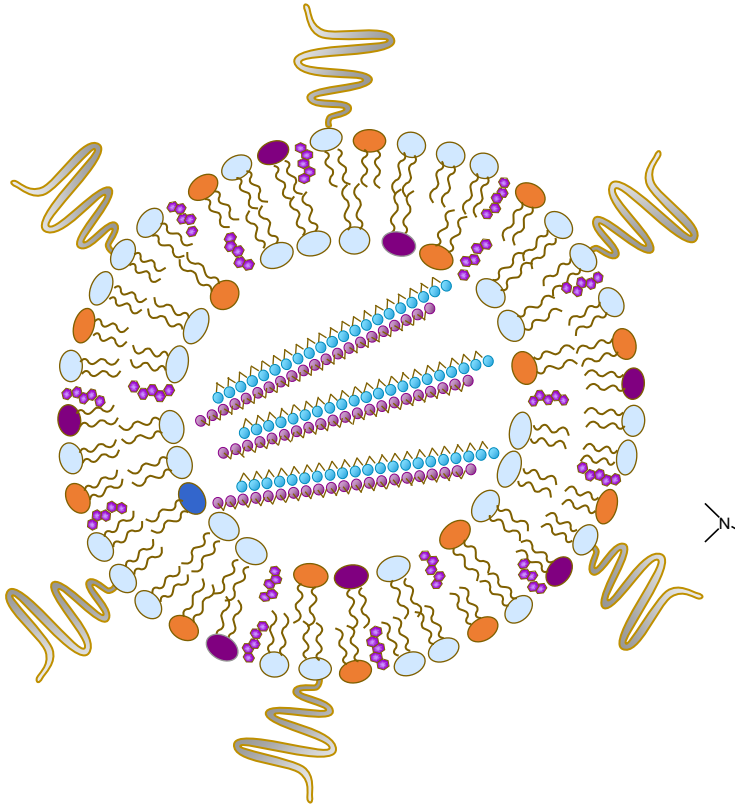

The Translational and Regulatory Development of an Implantable Microdevice for Multiple Drug Sensitivity Measurements in Cancer Patients



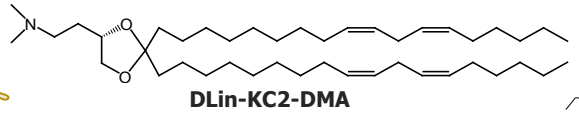
Small molecules

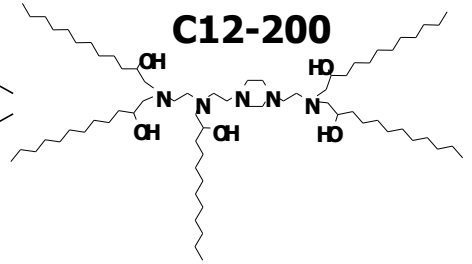
Genetic therapy (e.g., siRNA, mRNA)

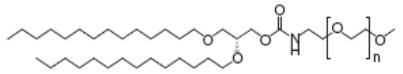
The most clinically advanced delivery systems for RNAi and mRNA are lipid and lipid-like nanoparticles (LNPs)

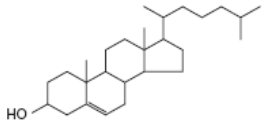


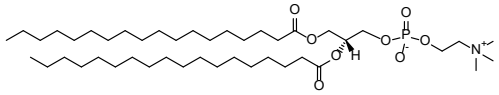
- Multi-component lipid formulation
  - Ionizable* cationic lipid
  - Structural lipid
  - PEG lipid
  - Cholesterol











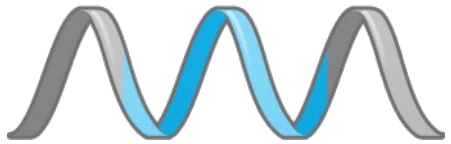
Low surface charge

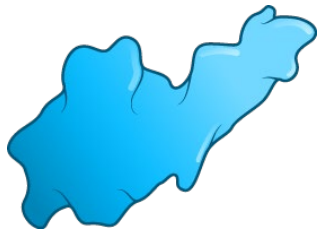
Small uniform size particle <100 nm

Pack et al, Biotech Bioeng, 2000; Semple et al, BBA, 2001

Central Dogma of Molecular Biology

DNA → messenger RNA → Protein



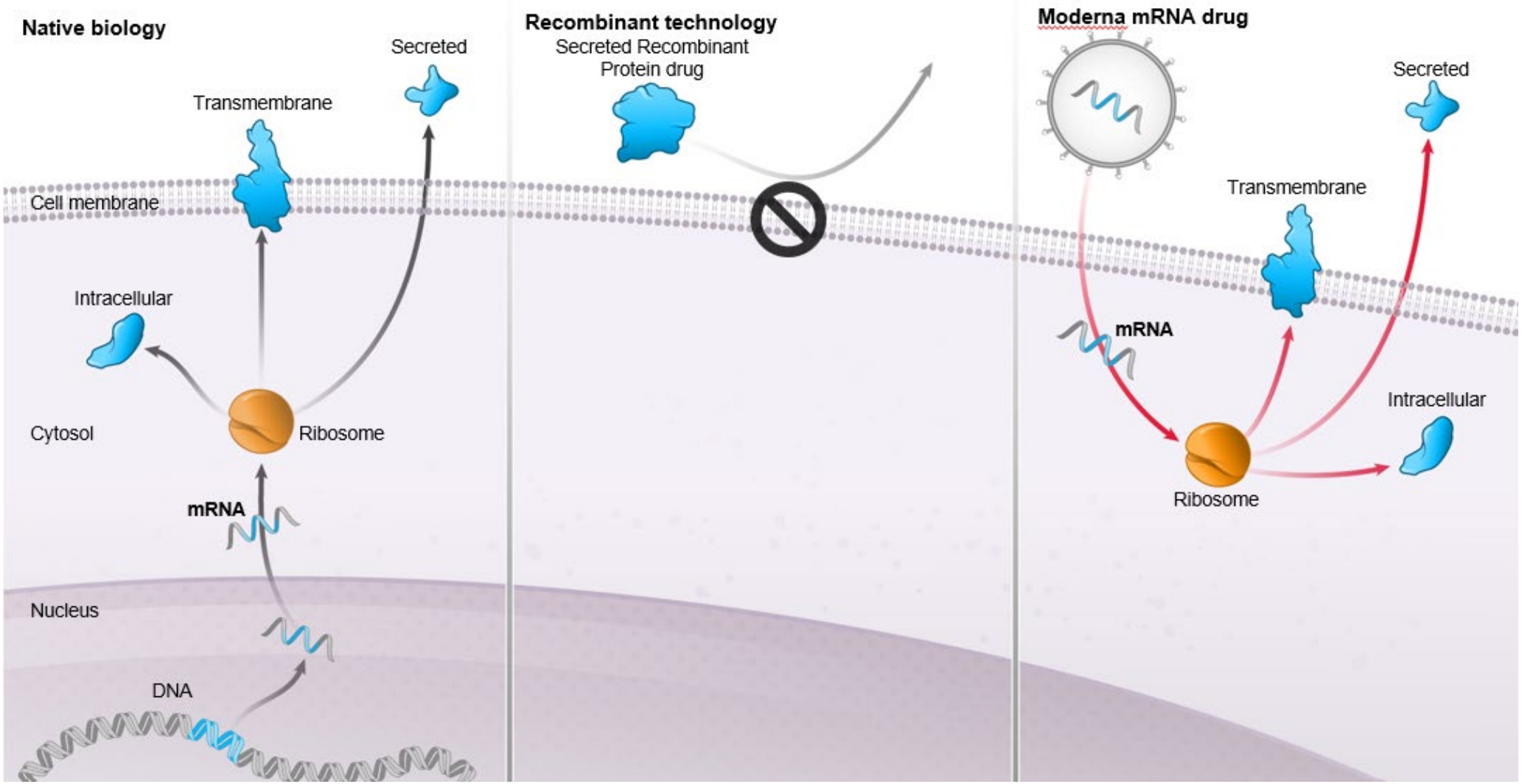


Hard Drive
DNA stores our genetic information

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

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

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



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

2. A single-step immunization by sustained antigen release.
J. of Immuno. Meth., 28: 193-197, 1979. Pharmacokinetics of antigen release from liposomes, PNAS, 88,10040,1991

3. PEG coatings, Science, 263: 1600,1994

4. Ionizable components
Biotechnology and Bioengineering, 67: 217,2000. PNAS, 98: 1200, 2001

5. Library of Lipids, Nature Biotechnology, 26: 561, 2008

6. Microfluidic Manufacturing of Drug Delivery Nanoparticles, Nano Letters, 8: 2906, 2008

Moderna COVID19 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)

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

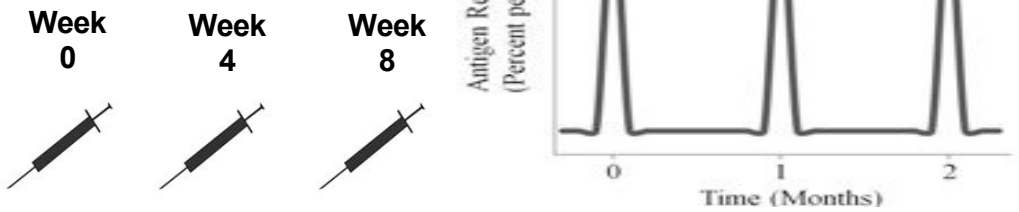
- At 2 years, risk of recurrence or death reduced by 44% (one-sided p value=0.0266)

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

Single injection vaccine delivery technology for ***self-boosting or long-acting vaccines***

Approach: Develop a microparticle platform that confers immunity after a single injection by mimicking current vaccination regimens

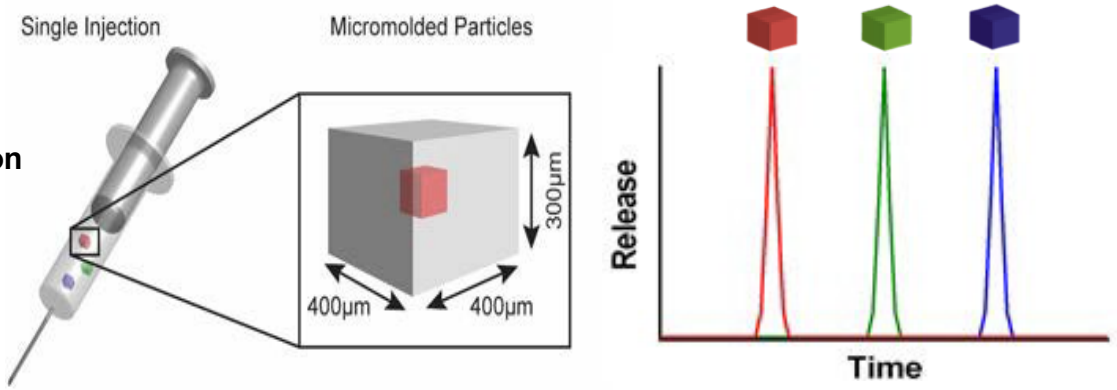
Current Vaccination Schedule



Advantages:

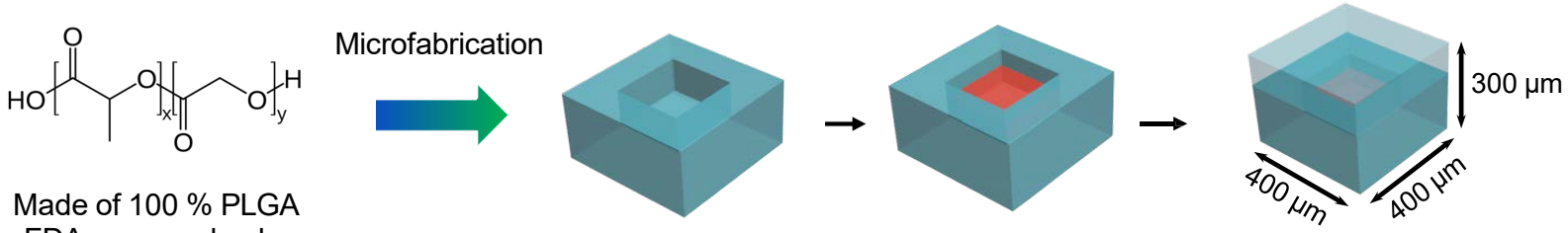
1. Reach herd immunity quicker due to improved compliance
2. Obtain higher and more sustained titers
3. Decrease the chances of variant's having a chance to occur due to 1 and 2

Single-injection Vaccination



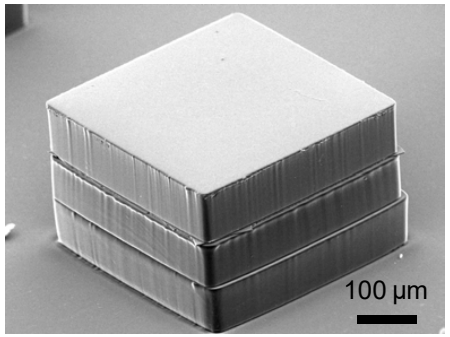
McHugh et al., *Science* 2017;357:1138.

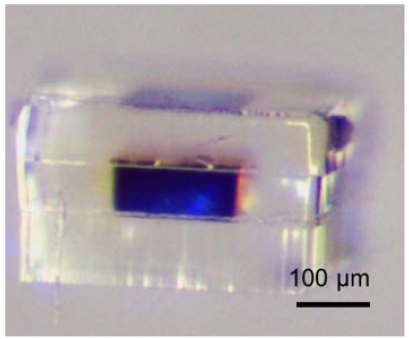
Micromolded particles using PLGA

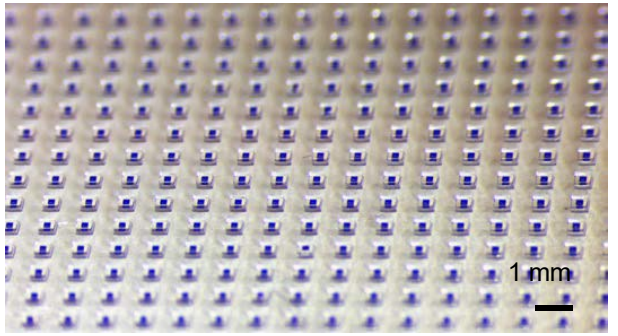


Made of 100 % PLGA
an FDA-approved polymer

Particle base | Filled particle | Sealed particle



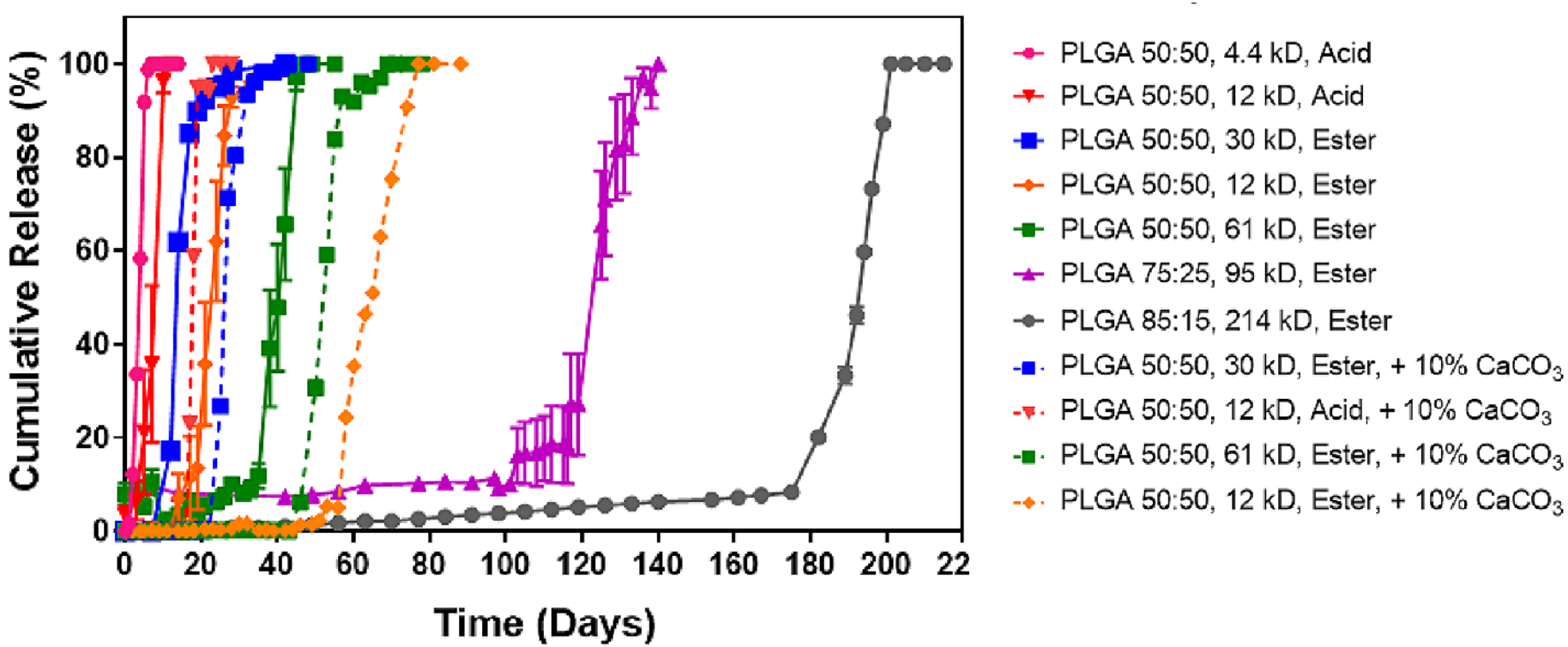




We could encapsulate a wide range of vaccines, including inactivated viruses, recombinant proteins, nucleic acids, etc.

"Fabrication of fillable microparticles and other complex 3D microstructures."
Science, **2017**, 357, 1138

in vivo vaccine release



Microneedle patches for vaccination