Finding the Sweet Spot in BioTechology

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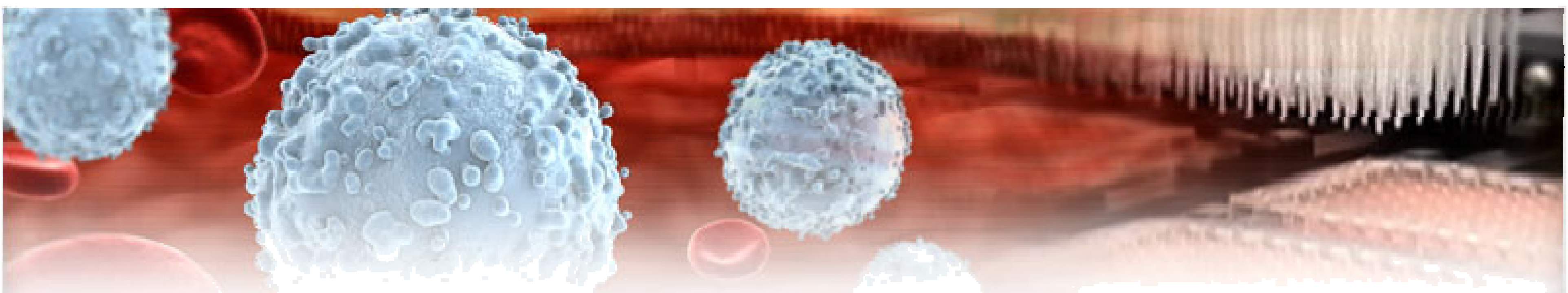
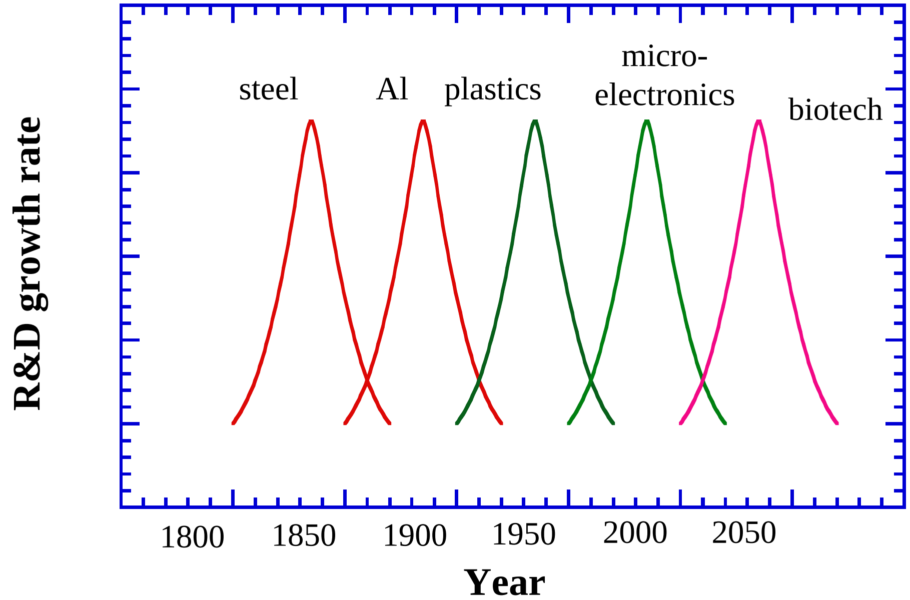
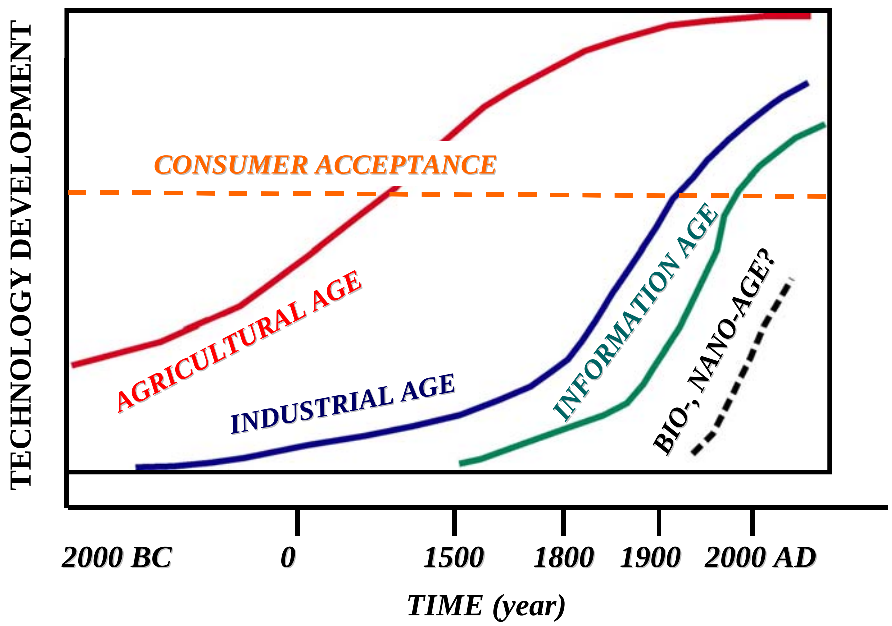


From Cells to Engineering to Automation to Products

What's gonna be the next technological revolution?





Can Anything be Learned or Predicted from Prior Inventions?

Digital biology?

Telephone
1876

Telegraph
1838

Wireless
1895

Radio
1907

Television
1923

Radar
1936

Computer
1941

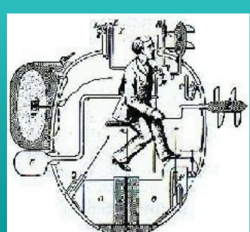
Communication
Satellite
1958

Personal
Computer
1977

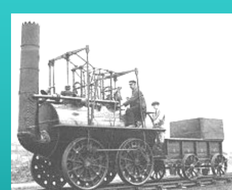
1600 1700 1800 1900 2000

Distributed bio-power, Teleportation?

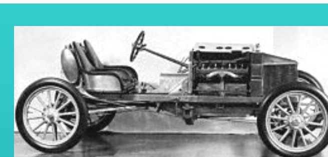
Submarine
1624



Locomotive
1802



Steamship
1807



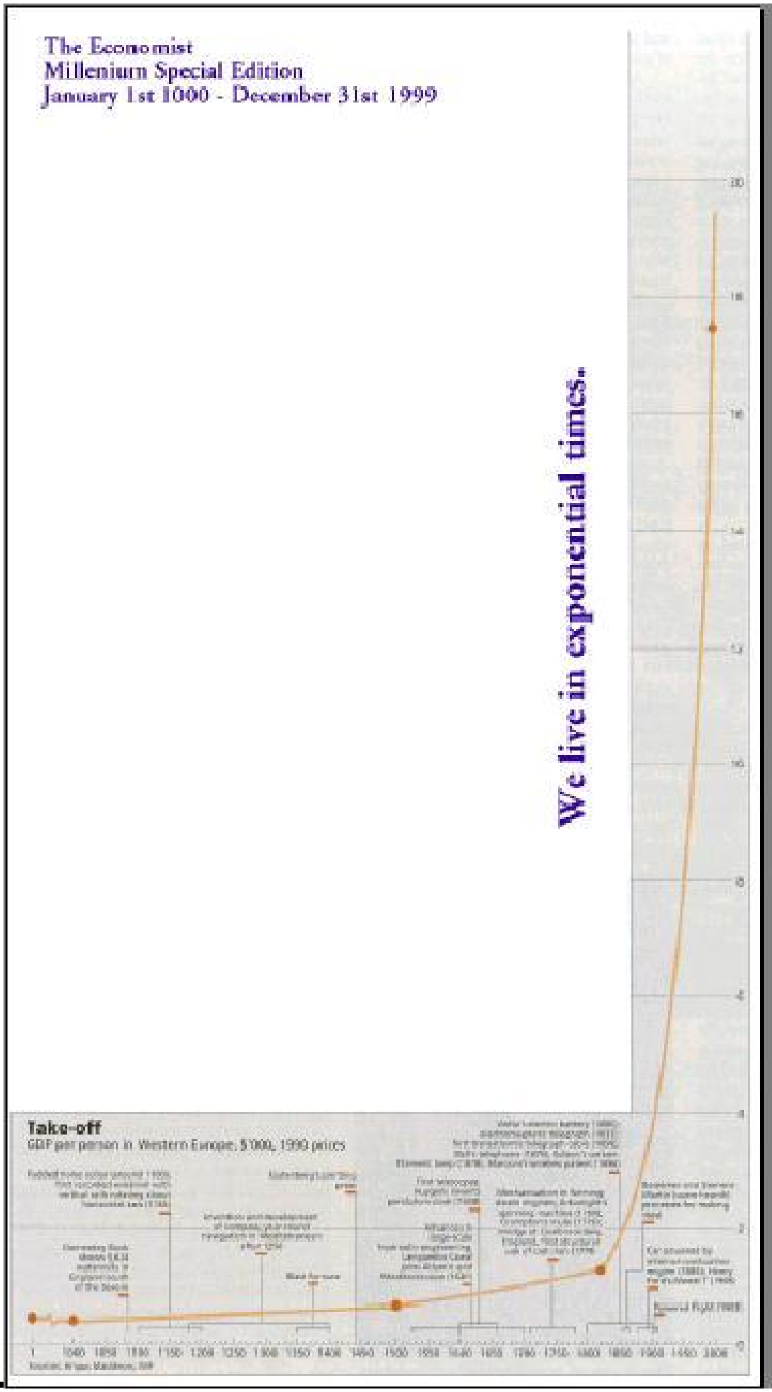
Automobile
1889

Airplane
1907

Jet
1928

Helicopter
1940

1600 1700 1800 1900 2000



World Economic Performance Was Sparked by "One" Event

GDP Per Capita in Western Europe, 1000 – 1999 A.D.

This curve looks quite smooth on a macroscopic scale.

Notice the "knee of the curve" occurs at the industrial revolution, circa 1850.

Can Anything be Learned or Predicted from Prior Inventions?

Personalized medicine, cure for common cold, herbal medicine, broad-range immunotherapies, body parts on demand?

VAXDESIGN

One Good Idea Makes the Difference

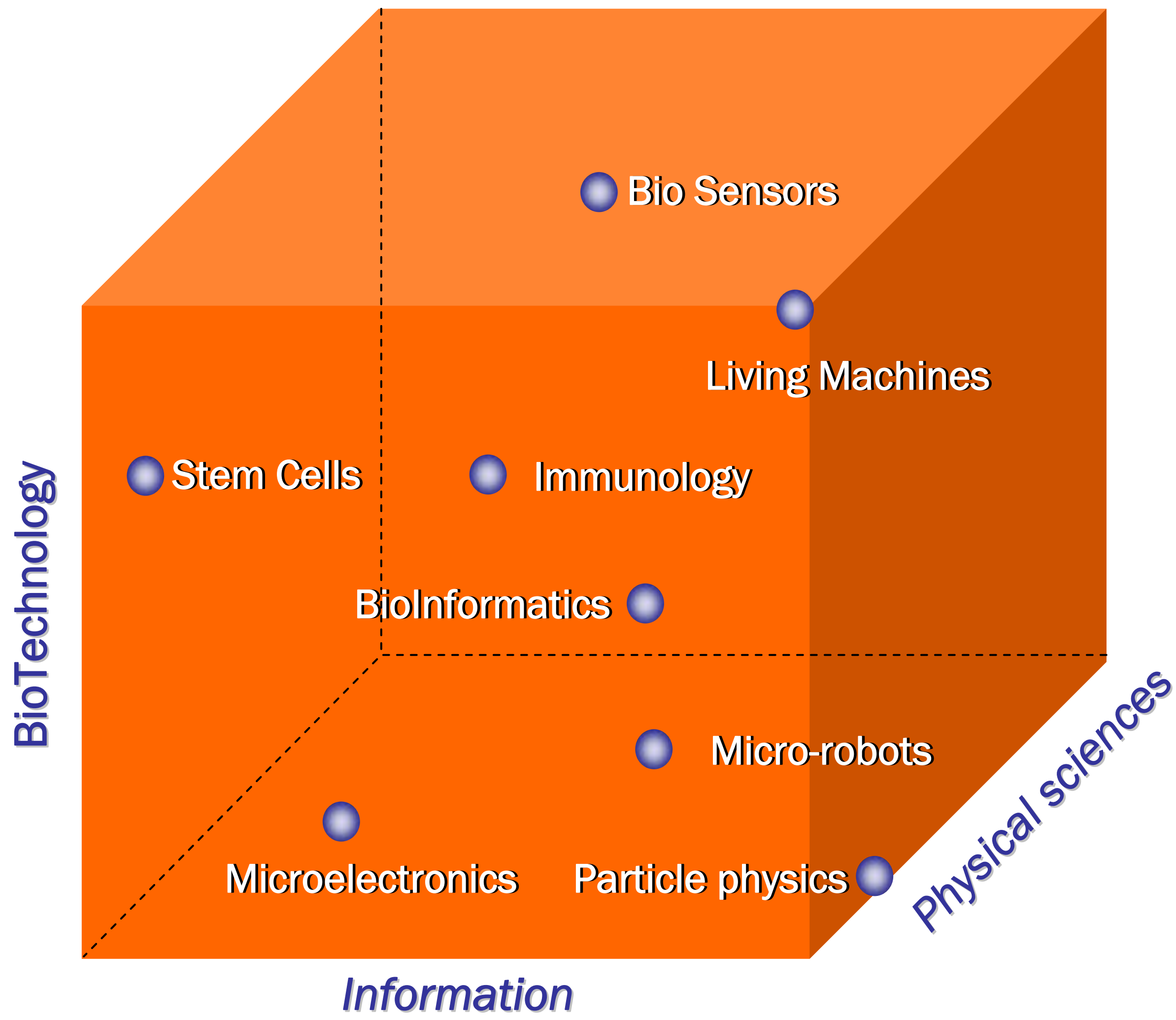
- Industrial revolution was an amalgam of ideas about machines to manufacture or to move quickly on the earth.

- Flood of ideas in the 19th century, but none would have been realized without Watt's steam engine.

- The internal combustion engine made the 20th century industrial revolution continue (Brayton, Otto)

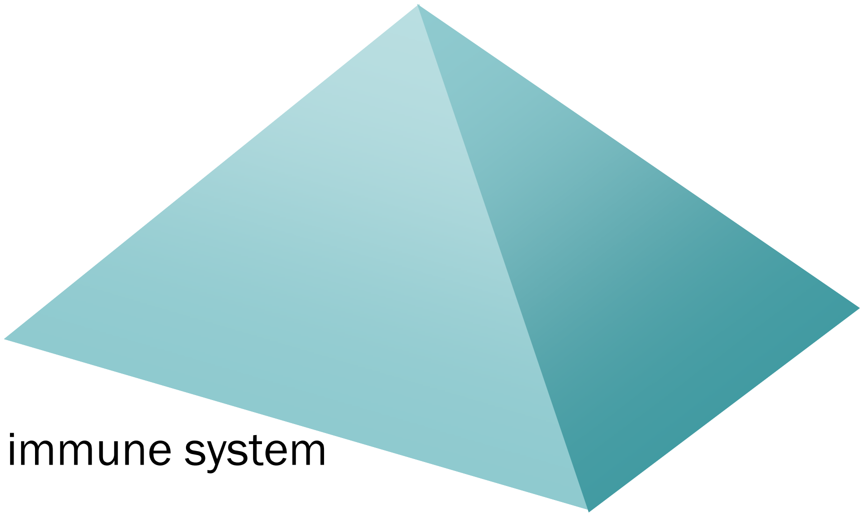
- Has there been that one good concept to make a difference in biotech? (tissue engineering, recombinant DNA technology, self-assembly, stem cells, nanoscience, ...)

The Future: Amalgascience - Coordination With Other Disciplines



Biotech/Tissue Engineering Opportunities

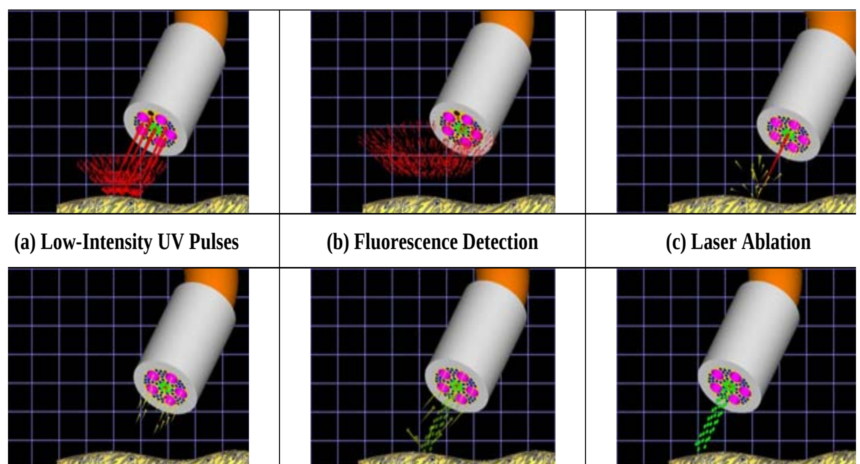
Interaction statistics: digital biology



Detect: rare event imaging

Diagnostics: artificial immune system

Cure: creation of neo-organs *in vivo*

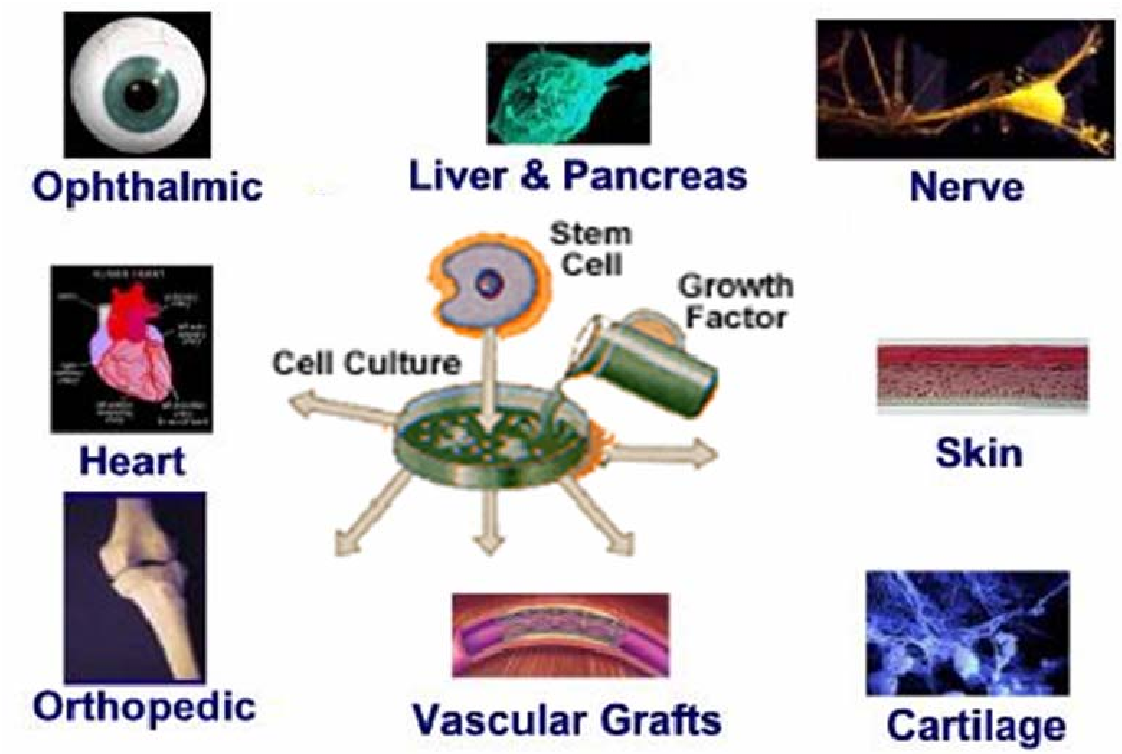


(a) Low-Intensity UV Pulses
(b) Fluorescence Detection
(c) Laser Ablation
(d) Material Removal
(e) Saline Flush Removal
(f) Deposition

The Question…

How can one, short of reproduction, reproducibly build a biocompatible structure that replicates the natural living system (microenvironment, 3D structure, vascularization, etc.) to support normal cell development?

Part of the Answer: Tissue Engineering



Problems:

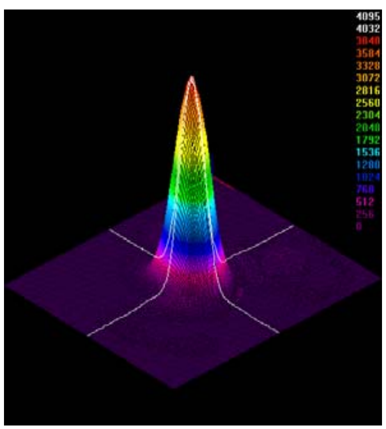
- Largely 2D
- No cellular, biomolecule nor biomaterial geospatial control
- No “zone” control in the z direction
- No customization

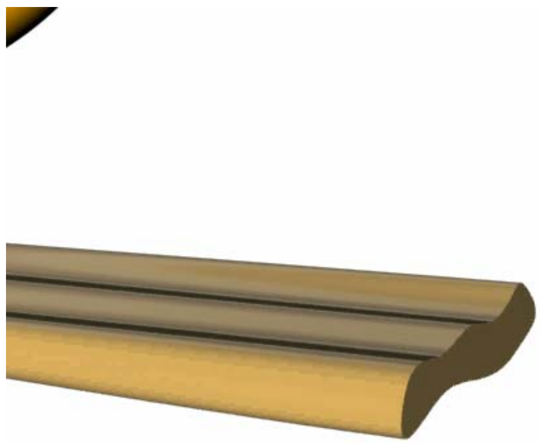
Therefore – hard to replicate the endogenous tissue

http://www.pittsburgh-tissue.net/about_te/index.html

InVivo Biological Architectural Tool

Utilize fundamental advancements in minimally invasive surgery [MIS], tissue engineering, and digital printing CAD/CAM techniques to create customized body parts by allowing the surgeon to build tissues from within



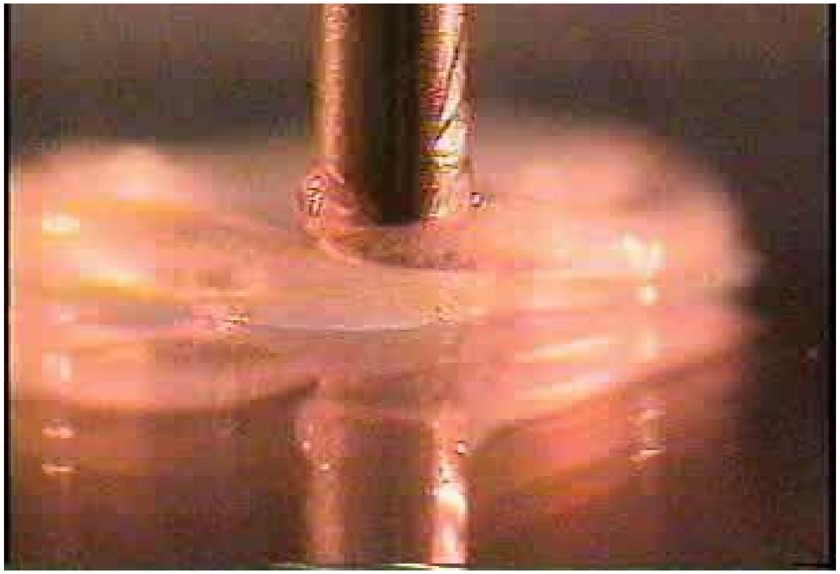


Physics issues:

- Fine deposition
- Nozzle design
- Actuation (macro to micro)
- Motor control
- Fiber coupling fsec laser

Why Body Parts on Demand?

Various Printing Demonstrations:



<u>Physics issues:</u>

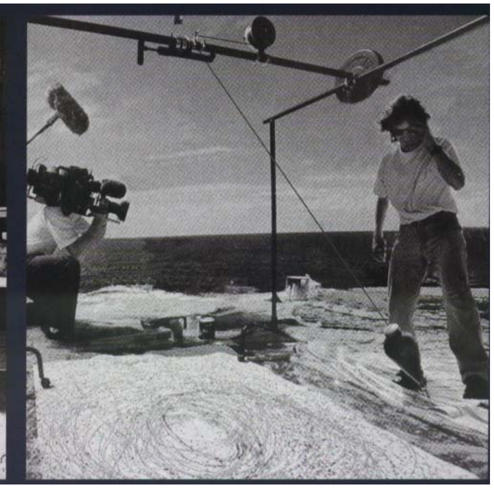
- Nozzle shear forces
- Mat'ls issues to build 3D structures
- Vision, imaging, feedback, & motion control

Truly Going from ART to PART

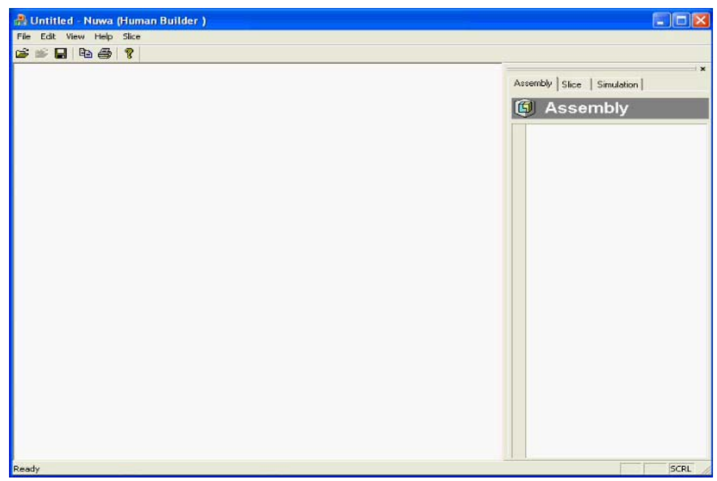
Fractal Painting

The Man

Direct-Painting

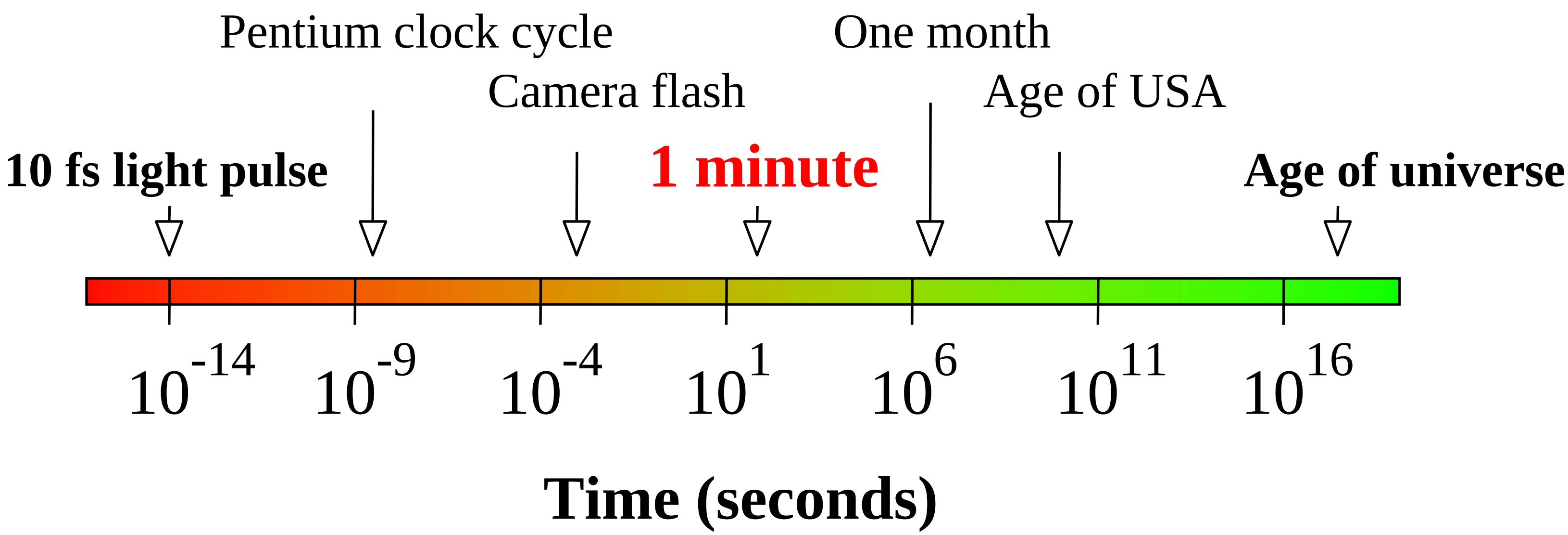


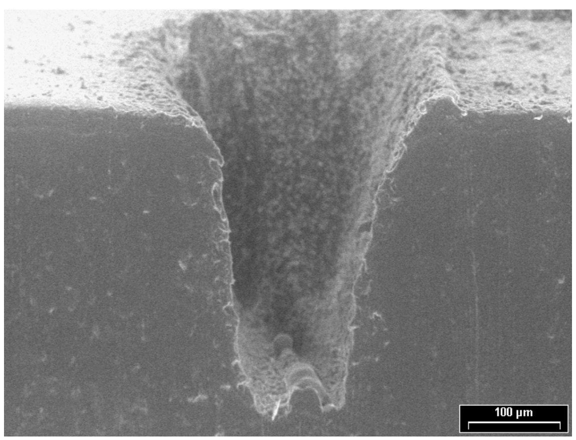
ART to Tissue Engineered PART

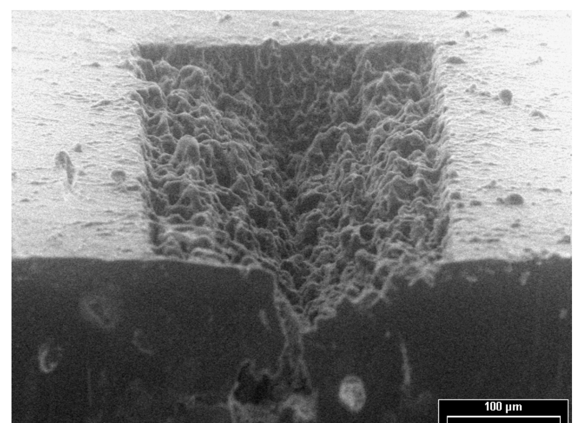


Ultra-Short Pulse Lasers

Femtosecond Time-Scales:

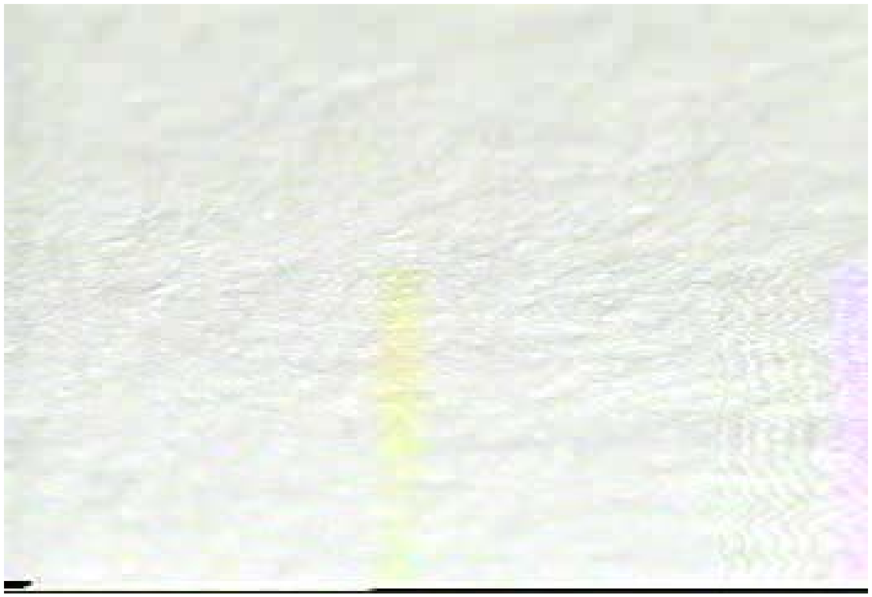




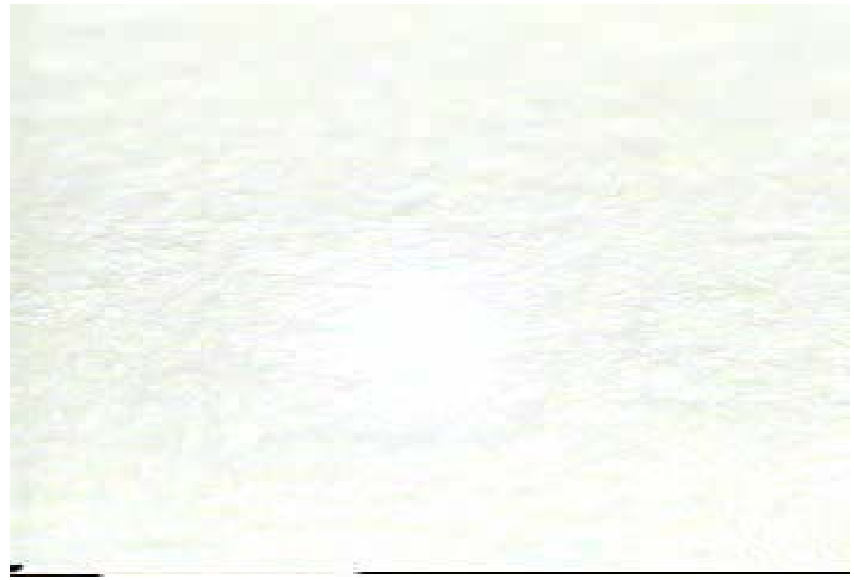


Laser Micromachining/Surgery

Micromachining on paper



Femtosecond machining



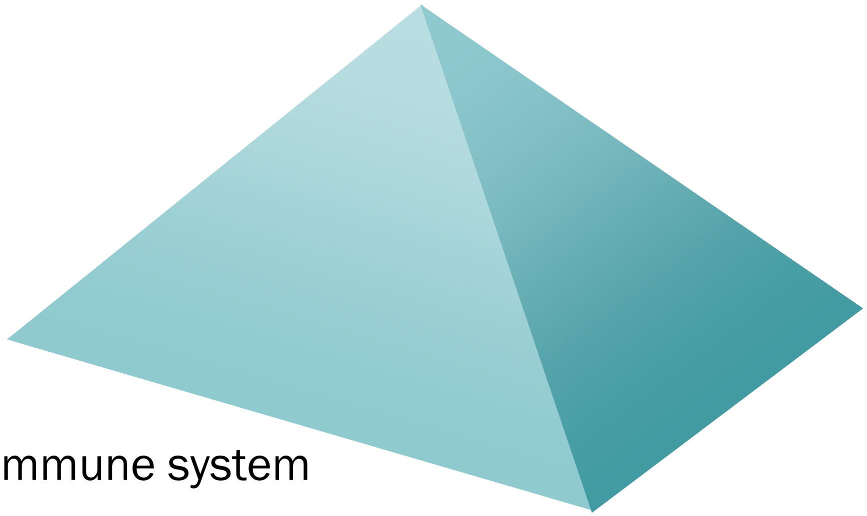
Nanosecond machining

Physics Issues:

- Waveguide designs
- Bending losses
- Diffractive optics

Biotech/Tissue Engineering Opportunities

Interaction statistics: digital biology

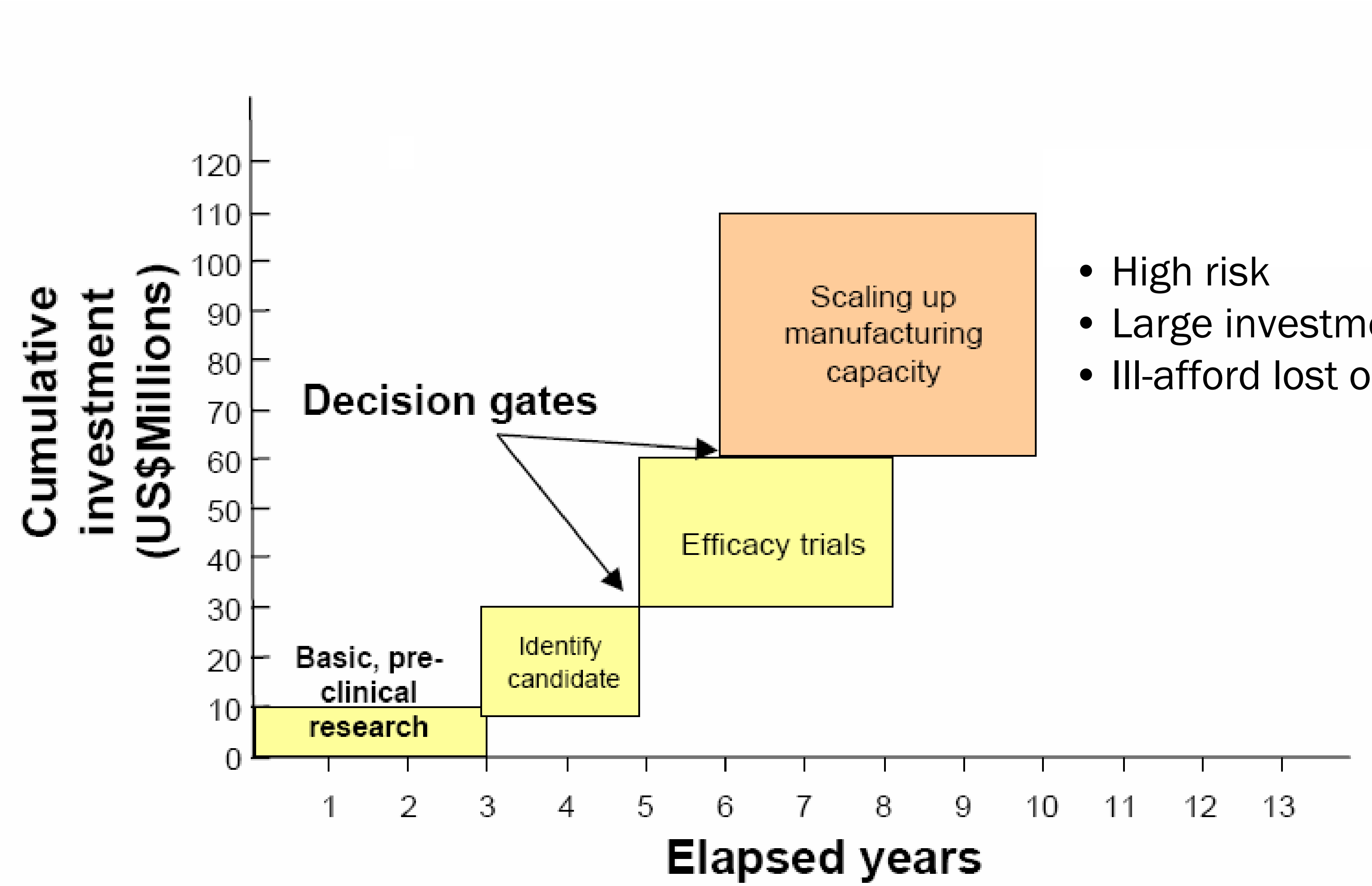


Detect: rare event imaging

Prevent: artificial immune system

Cure: creation of neo-organs *in vivo*

The Costs to Bring Immunotherapies to the Market



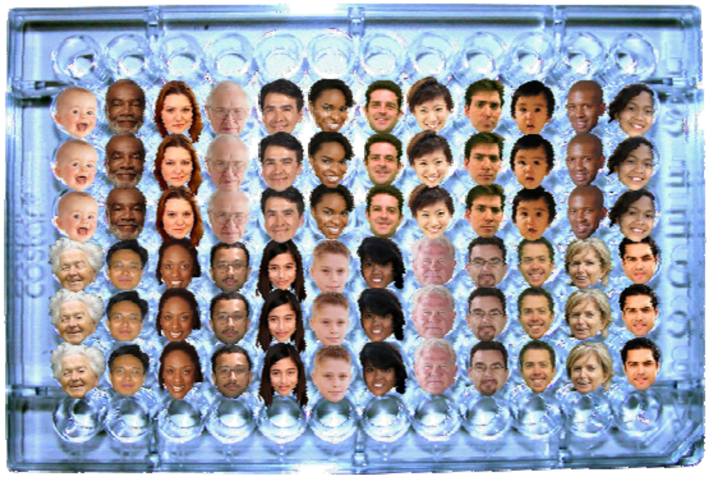
- High risk
- Large investment
- Ill-afford lost opportunity costs

http://www.vaccinealliance.org/site_repository/resources/21VacMarket.pdf

Challenging Disease and the Market Differently

1. Why it costs so much to bring drugs to the market?
   - Animals lie and exaggerate
   - Lost opportunity costs

2. How can you make money by accelerating the drug development process?
   - Find the bottleneck & turn the problem inside out
   - Create *in vitro* surrogate human immune systems



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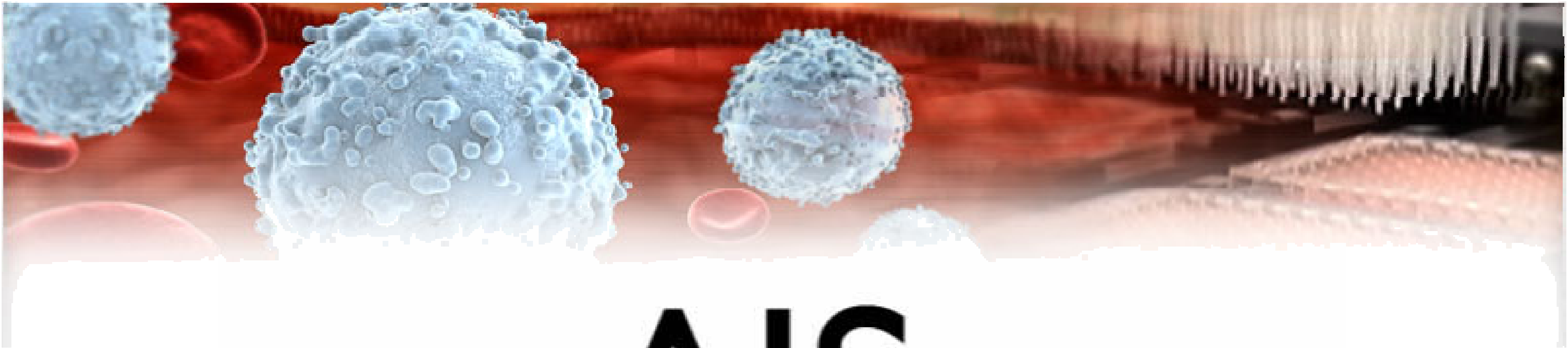
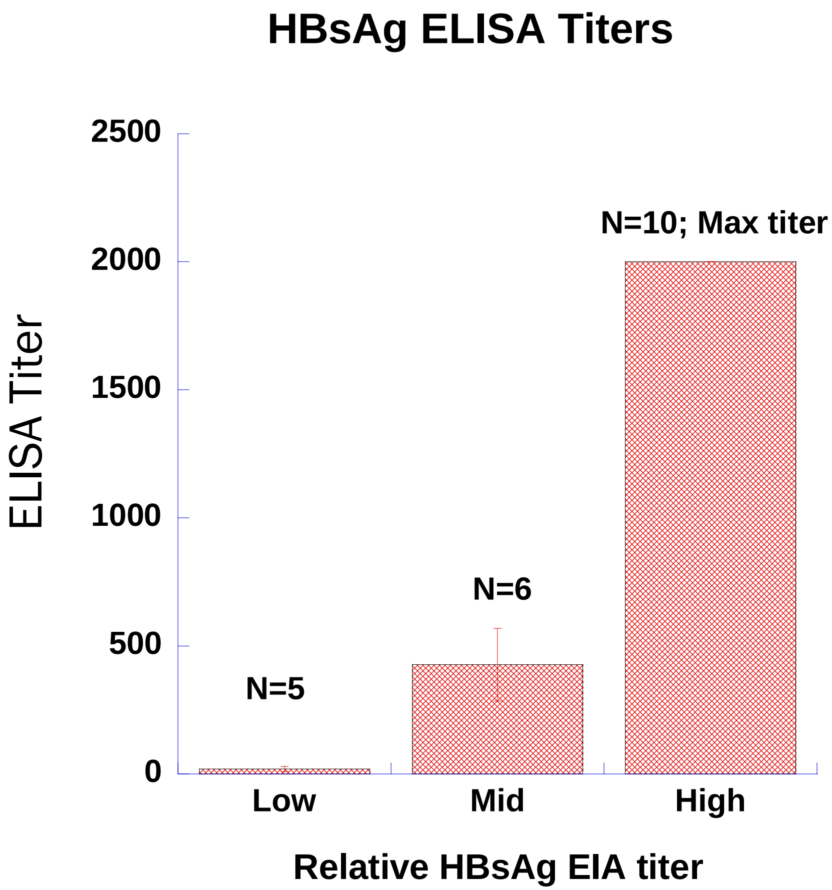


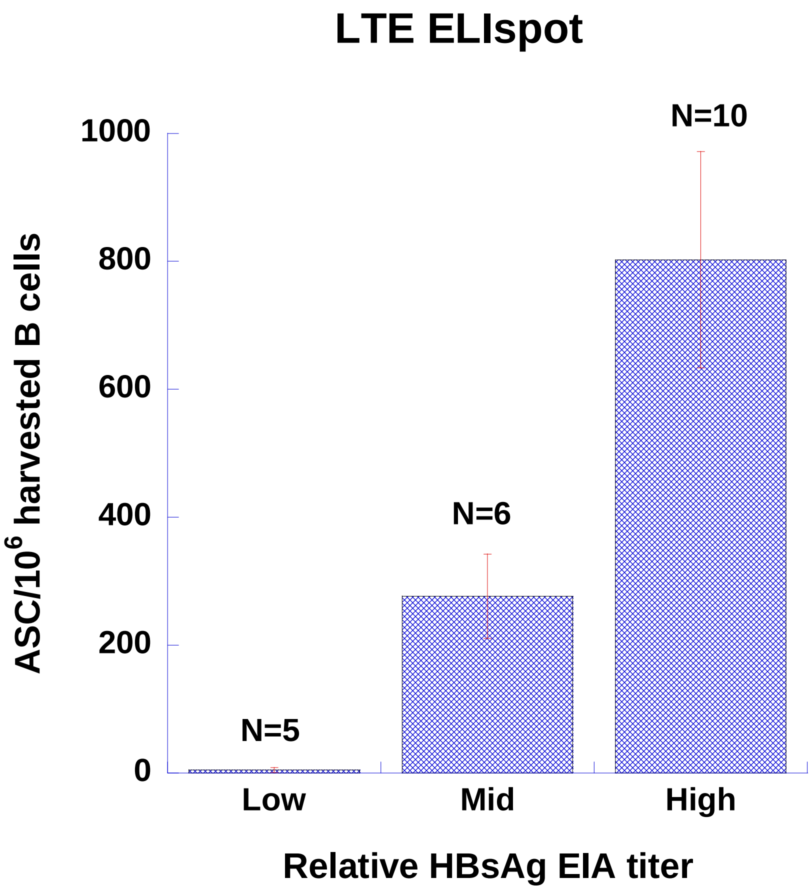
AIS

ARTIFICIAL IMMUNE SYSTEM

MODEL · PROCESS · AUTOMATION

Correlative Analysis of AIS Response vs Serum Titer for Hepatitis B





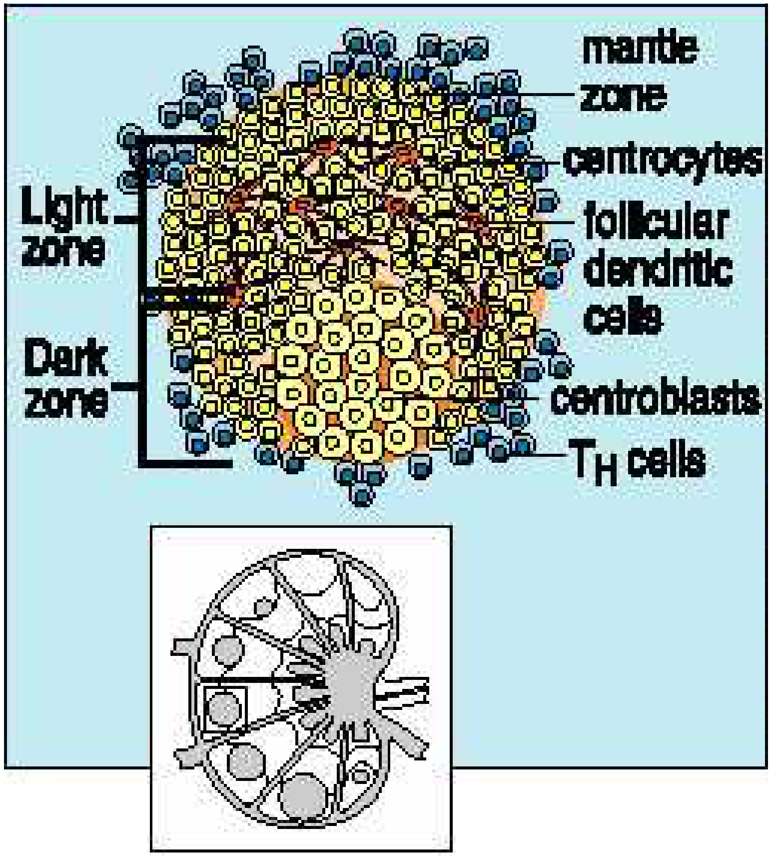
Serum titer groupings: Low 3-57.1; Mid 128-864; High 2000 or > 2000

Designing an *In Vitro* Biological System

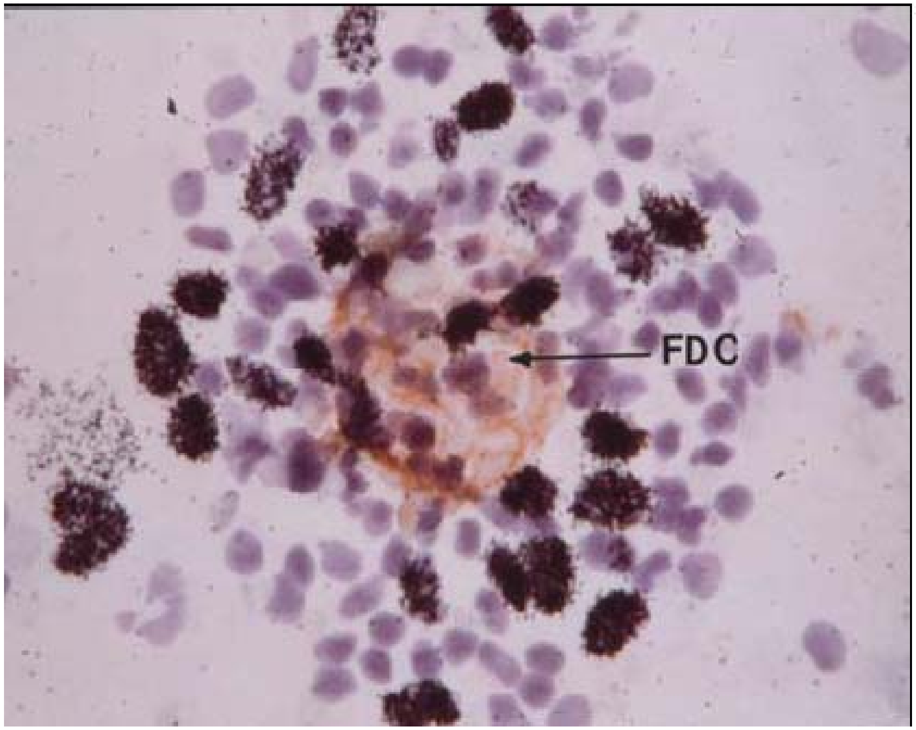
- How to mimic biology
  - don't give into the biologists
  - don't make it too simple
  - the right cells @ the right time @ the right place
- How to assemble biology
  - self-assembly
  - synthetic assembly
  - forced assembly

Self-Assembly of the Germinal Center

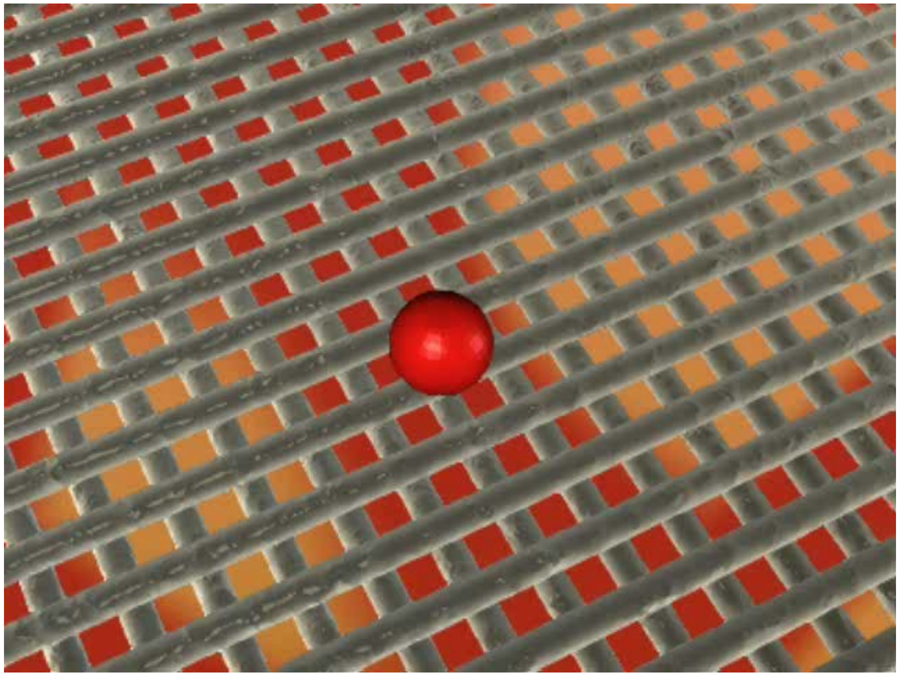
Schematic representation of a GC

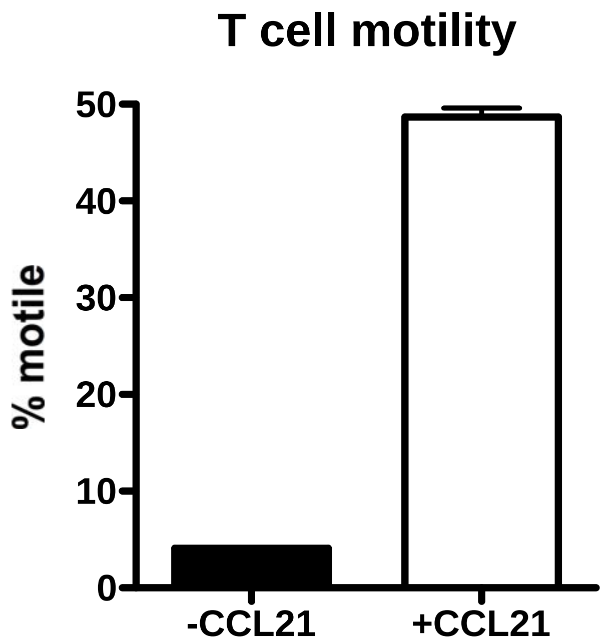


In vitro GC

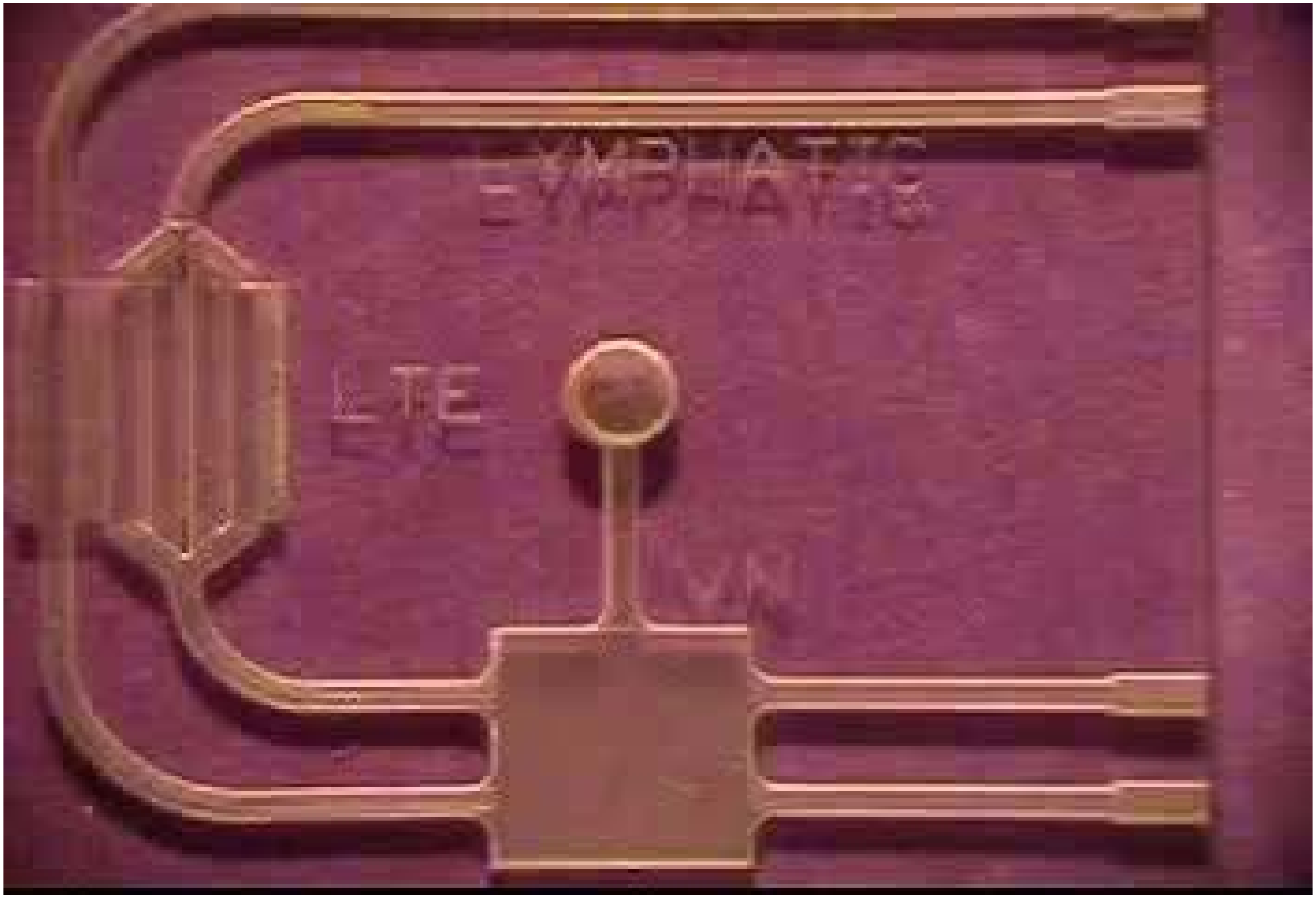


Synthetic Assembly of a Germinal Center

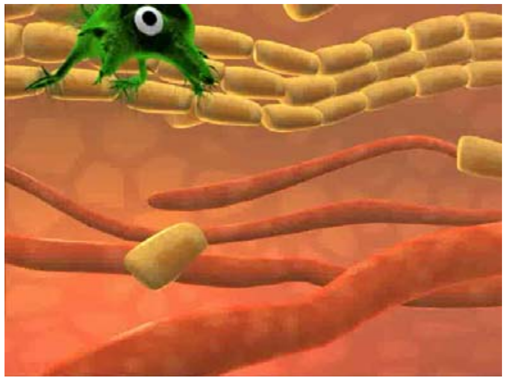


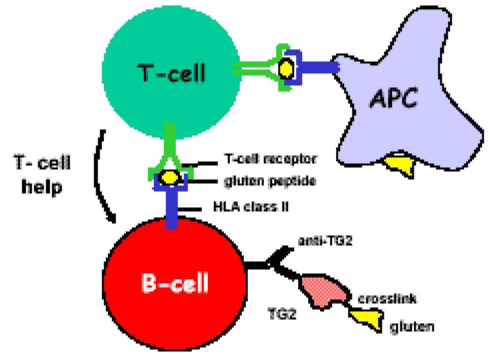


“Forced” Assembly



Biotech/Tissue Engineering Opportunities





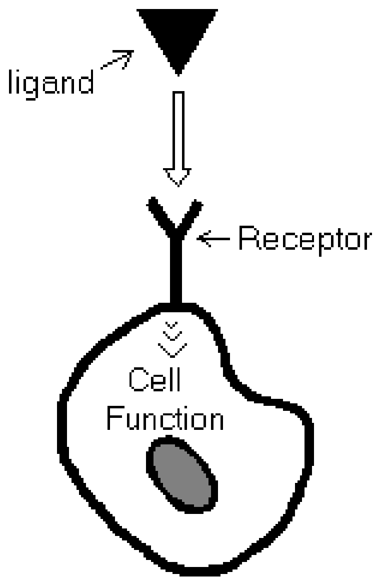
Interaction statistics: digital biology

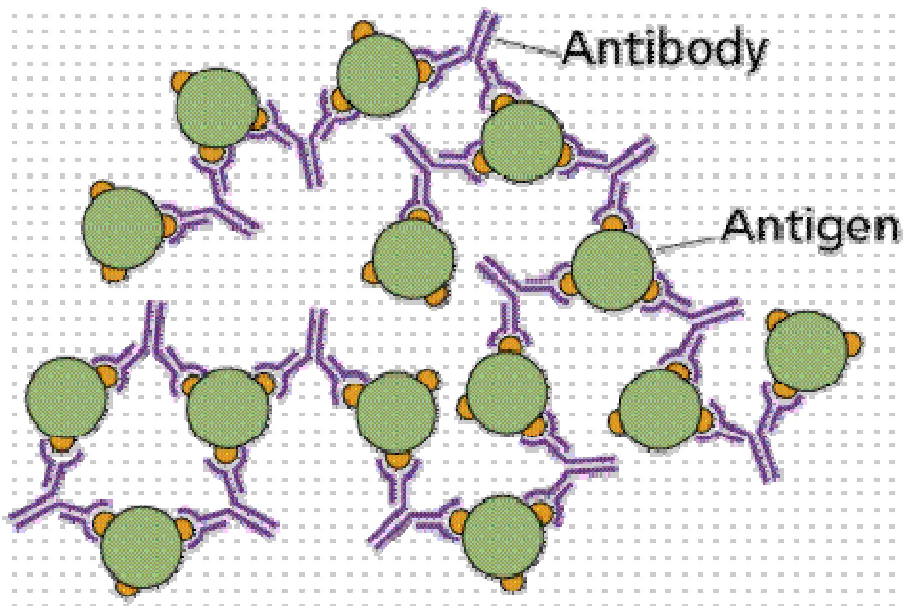
Detect: rare event imaging

Prevent: artificial immune system

Cure: creation of neo-organs *in vivo*

Challenge the Antigen/Antibody Physical Contact Model





The 3D structure of the ligand molecule, e.g. an antigen (agonist) matches the 3D structure of the antibody (receptor). This physical contact induces the cell function.

http://www.emc.maricopa.edu/faculty/farabee/biobk/antigenAB.gif

Physical Contact Model

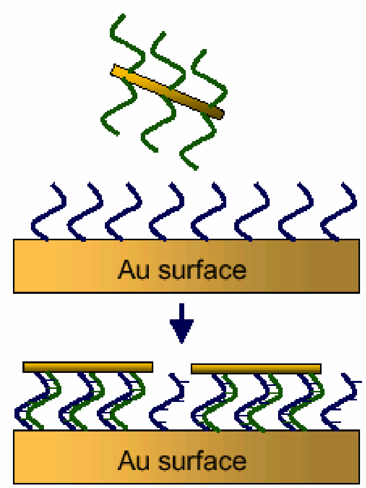
- Specific molecular interactions happen after random collisions between partners on a trial-and-error basis, using electrostatic, short range (two to three times the molecule size) forces.

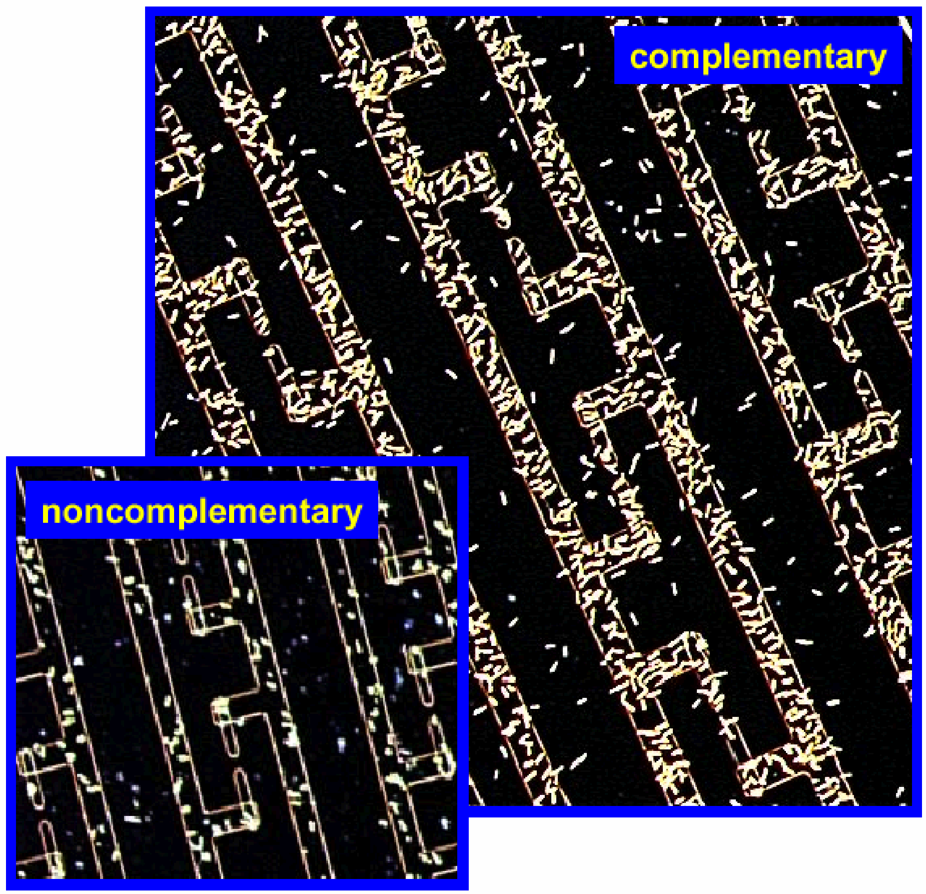
- But this kind of random encounter, amidst the bulk of molecules which are foreign to a given biochemical reaction, would give to these meetings statistically little chance of occurring.

- Thus, the simplest biological event might require a very long time to happen. This paradox is still unexplained by those adhering to this theory…

Short Range Interactions Do Not Satisfy i.e, they are all "wet"

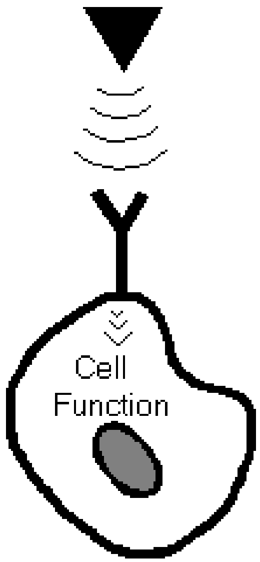
SS DNA and its complement act like psuedo "glue"





Tom Mallouk, Penn State University

If Not Physical Contact Alone, Could Electromagnetics Come to the Rescue?



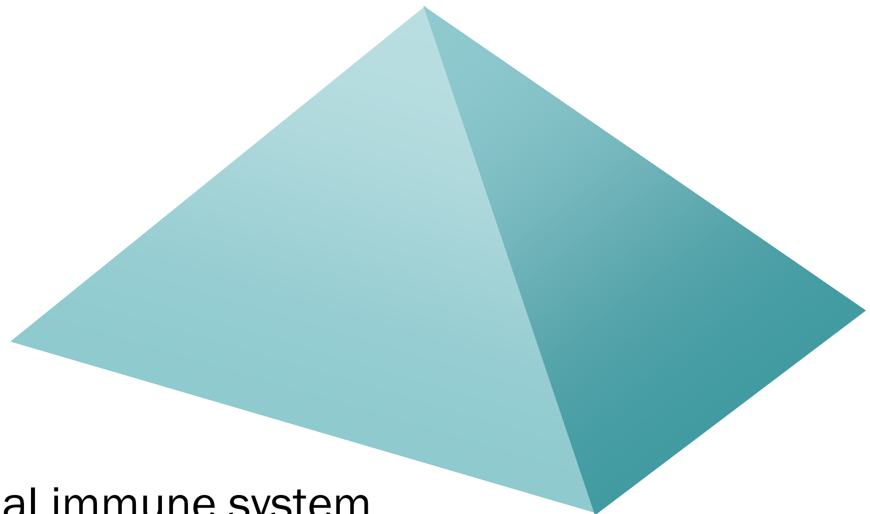
Small changes in the spectrum of a molecule (e.g. induced by a tiny structural change) would profoundly alter its resonating characteristics

Minute changes radically modify the molecular tertiary structure and function.

- phosphorylation,
- replacement of an ion by a similar one,
- switching of two peptides,
- 1 to 4 amino acid substitutions within HA can give rise to new viral strains

Biotech/Tissue Engineering Opportunities

Interaction statistics: digital biology



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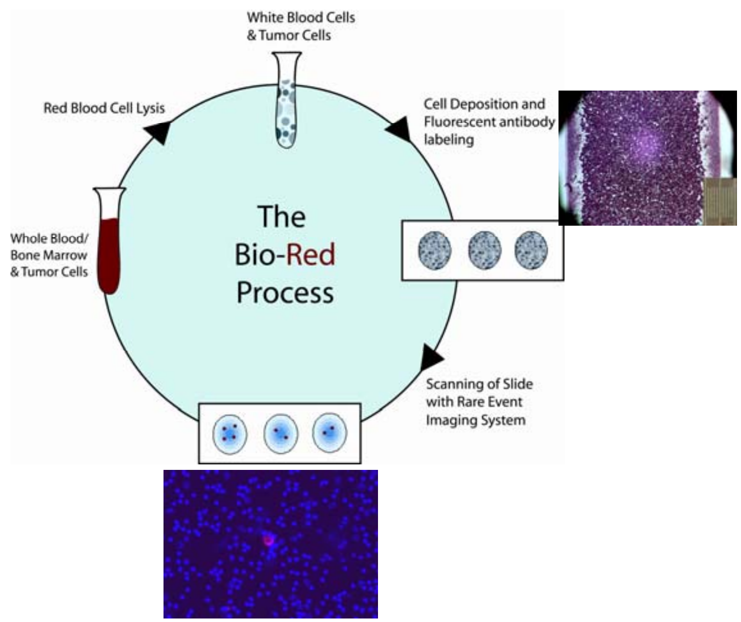


Prevent: artificial immune system

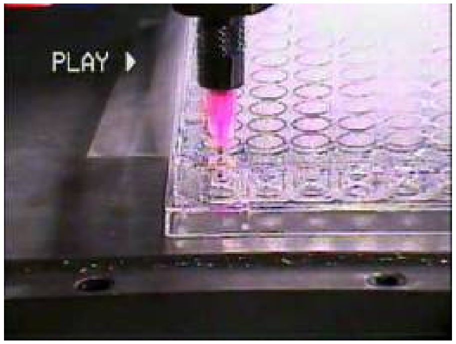
Cure: creation of neo-organs *in vivo*

Going from Science to Business

(1) building *in vitro* models & diagnositics, which will not require FDA approval

(2) manufacturing of the AIS constructs will occur via more automated processes in a cost effective manner

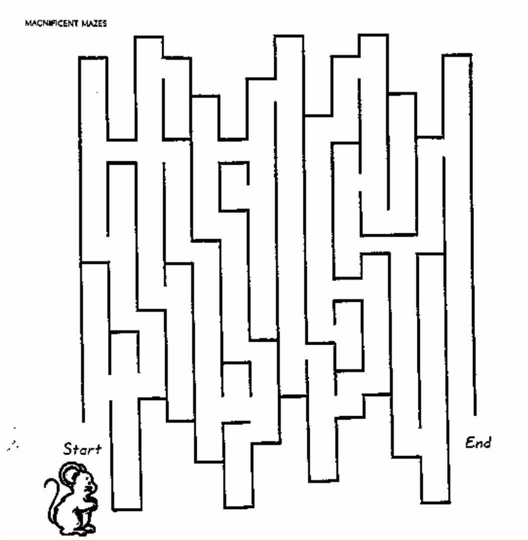
96 well format
automated
cost-effective
simple manufacturing



(3) the targeted market segments are the vaccine, cosmetics, big pharma, and chemical industries which are significantly larger and have deeper pockets than that of the burn and wound healing markets

Sometimes You Have To Think Differently – Turn the Problem Upside Down

Technical community is working on		A better approach is
• *in vitro* bioreactors	→	• *in vivo* bioreactor (human)
• *in vivo*/FDA approval	→	• *in vitro* models
• stopping an immune reaction	→	• inducing an immune response
• animal studies	→	• using surrogate models
• expensive nanoscience	→	• duct tape, ebay,
• manual processes	→	• automated processes
• centralized distribution	→	• distributed processes
• experts	→	• nature



This work was funded by DARPA/DSO in the
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