

At the Intersection of Nanotechnology and Bio-Pharma Convergence: What is a "Drug"- New Definitions, New Modalities?



U.S. Food and Drug Administration



August 2004

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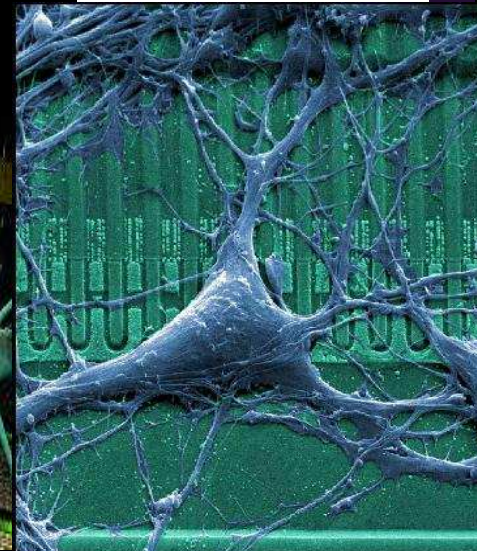
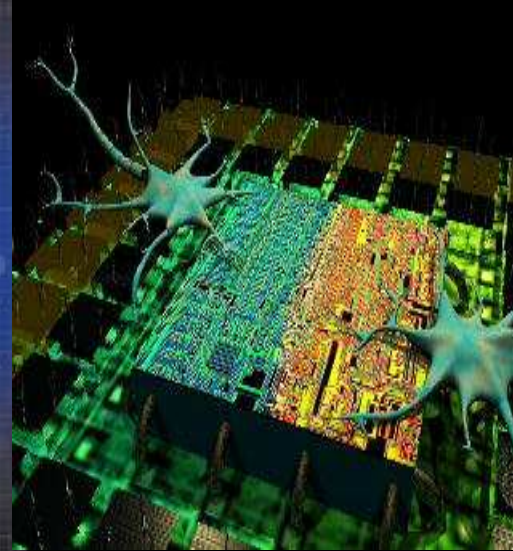
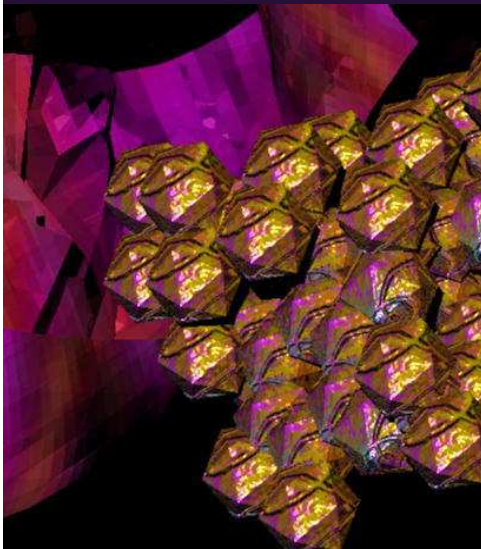
<http://www.nanosig.org/nanoelectronics.htm>

<http://www.technofutures.com/charles1.htm>



Synthetic Biology

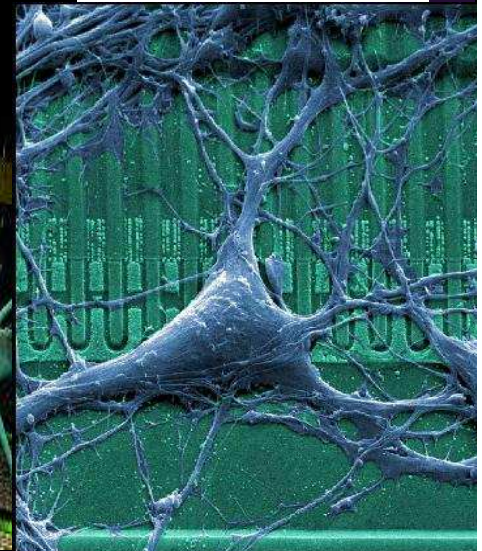
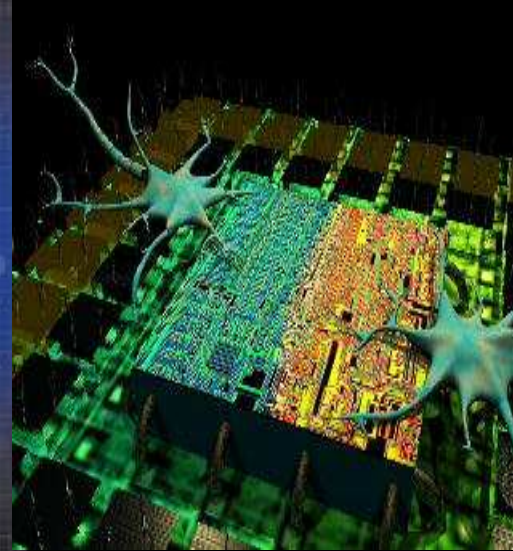
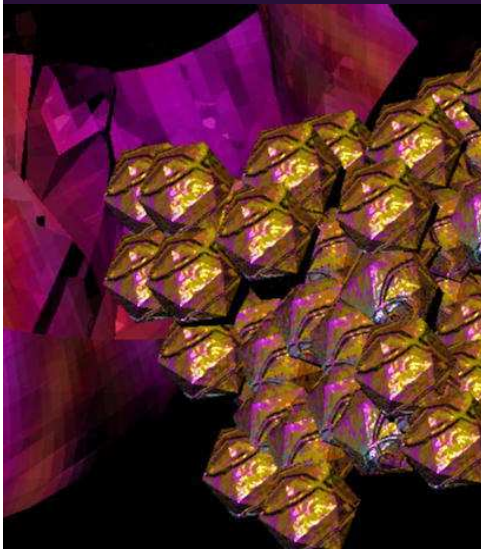
PHYSICAL
BIOSCIENCES
DIVISION



Define Nanotechnology - the precise patterning of matter at the molecular scale of interaction

Synthetic Biology

PHYSICAL
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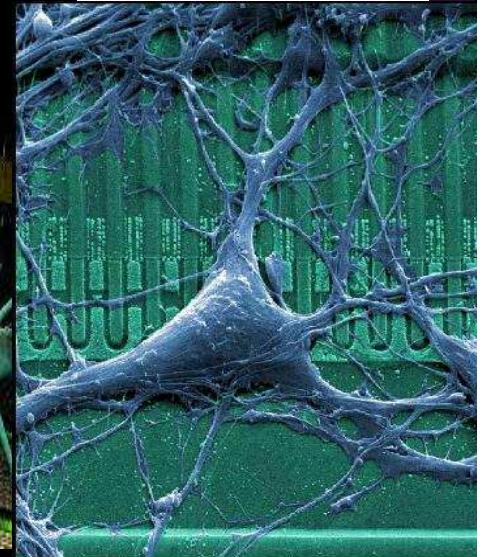
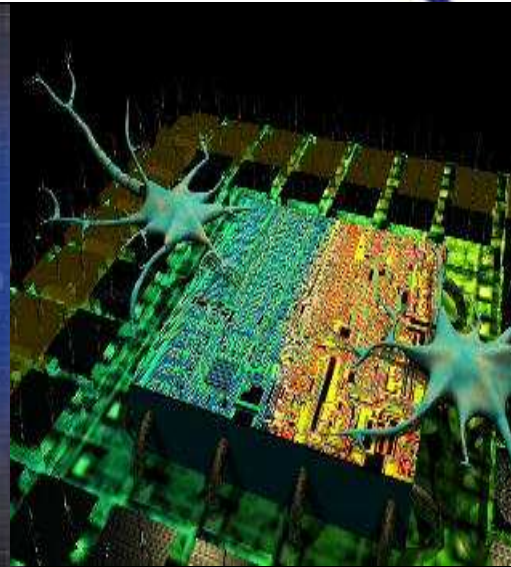
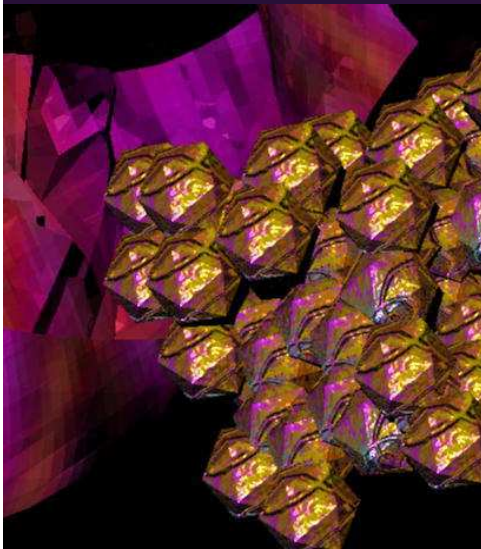


Define Nanotechnology - the precise patterning of matter at the molecular scale of interaction

Define Drug - substance used to cure, alleviate, diagnose, or prevent disease

Synthetic Biology

PHYSICAL
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Define Nanotechnology - the precise patterning of matter at the molecular scale of interaction

Define Drug - Device used to cure, alleviate, diagnose, or prevent disease

Post-Genomic
Society

Nanotechnology

Health Care
Future Map

Smart IT

Performance
Enhancement

The Emergent

Infotech / Biotech / Nanotech / Cognotech

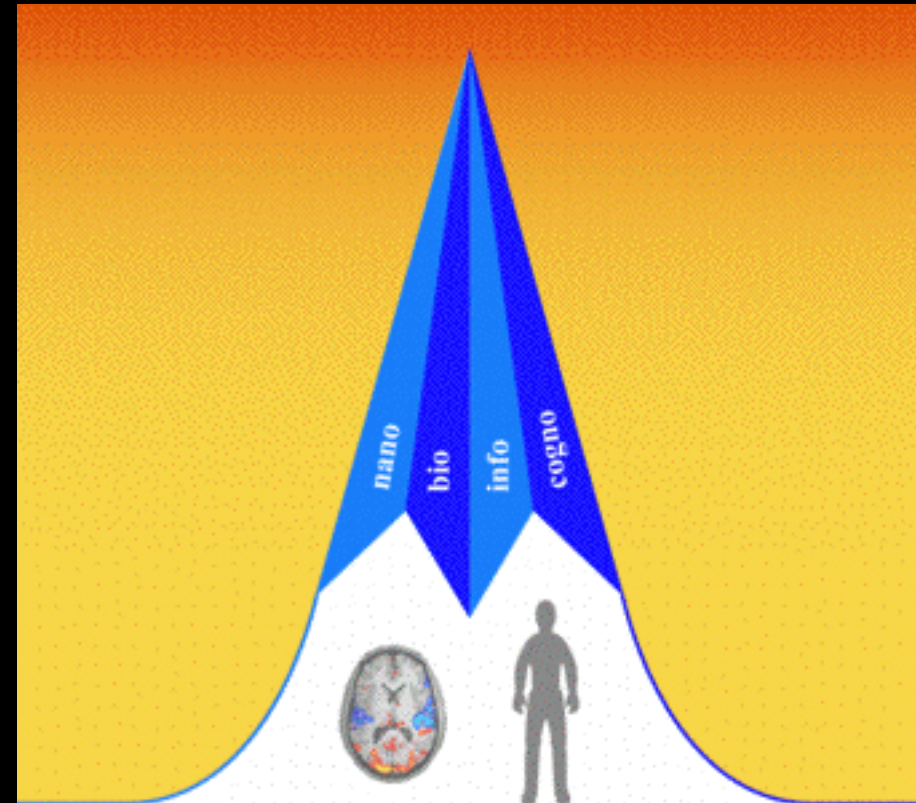
Operational Ecology

NBIC Conference

Converging Technologies
for Improving Human
Performance:

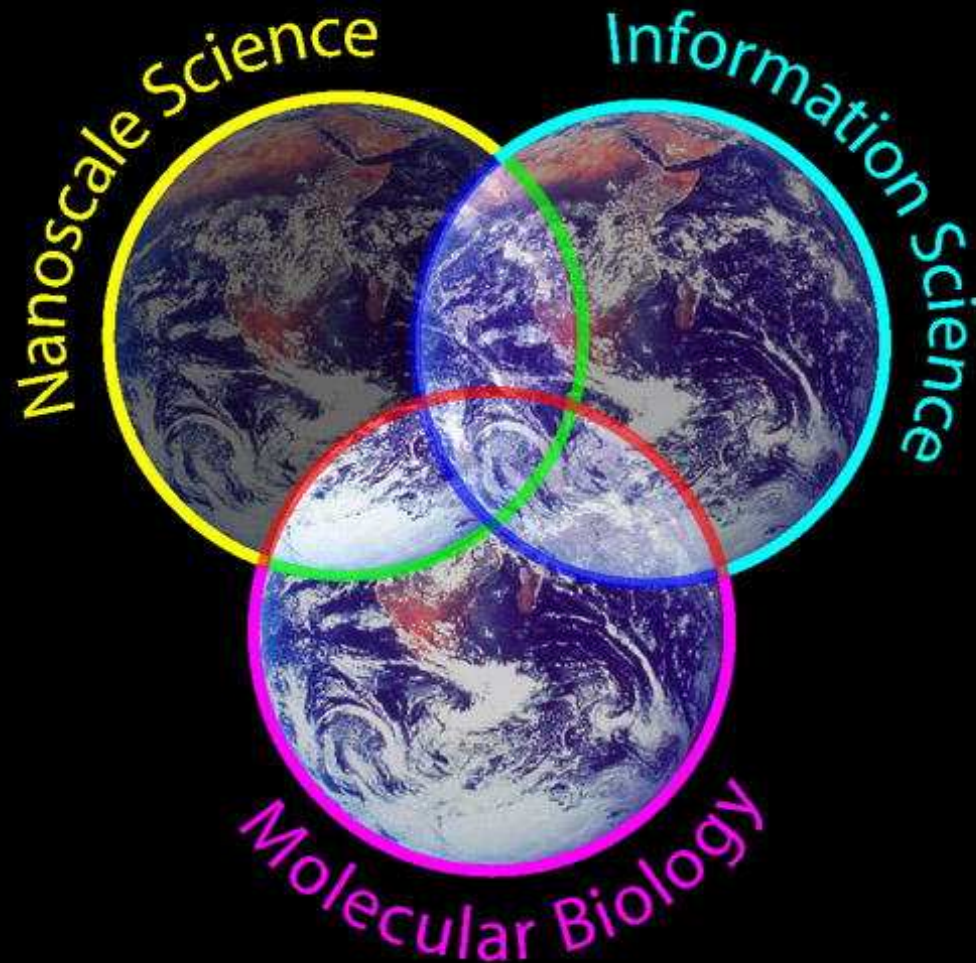
Nanotechnology,
Biotechnology, Information
Technology and Cognitive
Science

NSF/DOC-sponsored report
<http://www.wtec.org/ConvergingTechnologies>



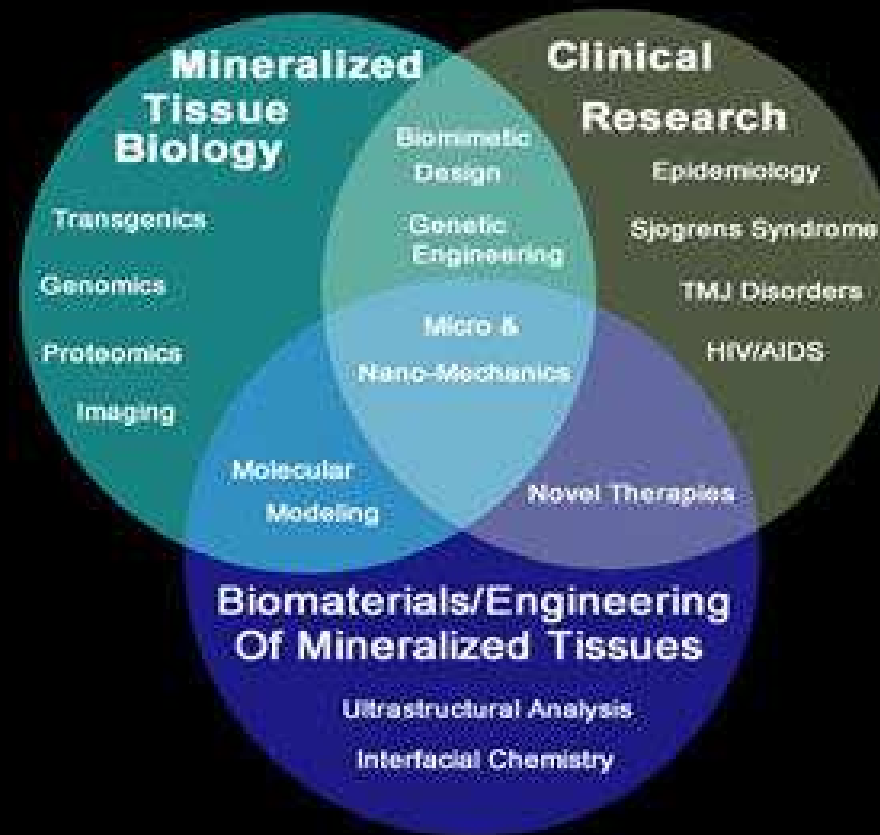
The Infotech / Biotech / Nanotech Convergence

NNI - National Nanotechnology Initiative



3/26/2010

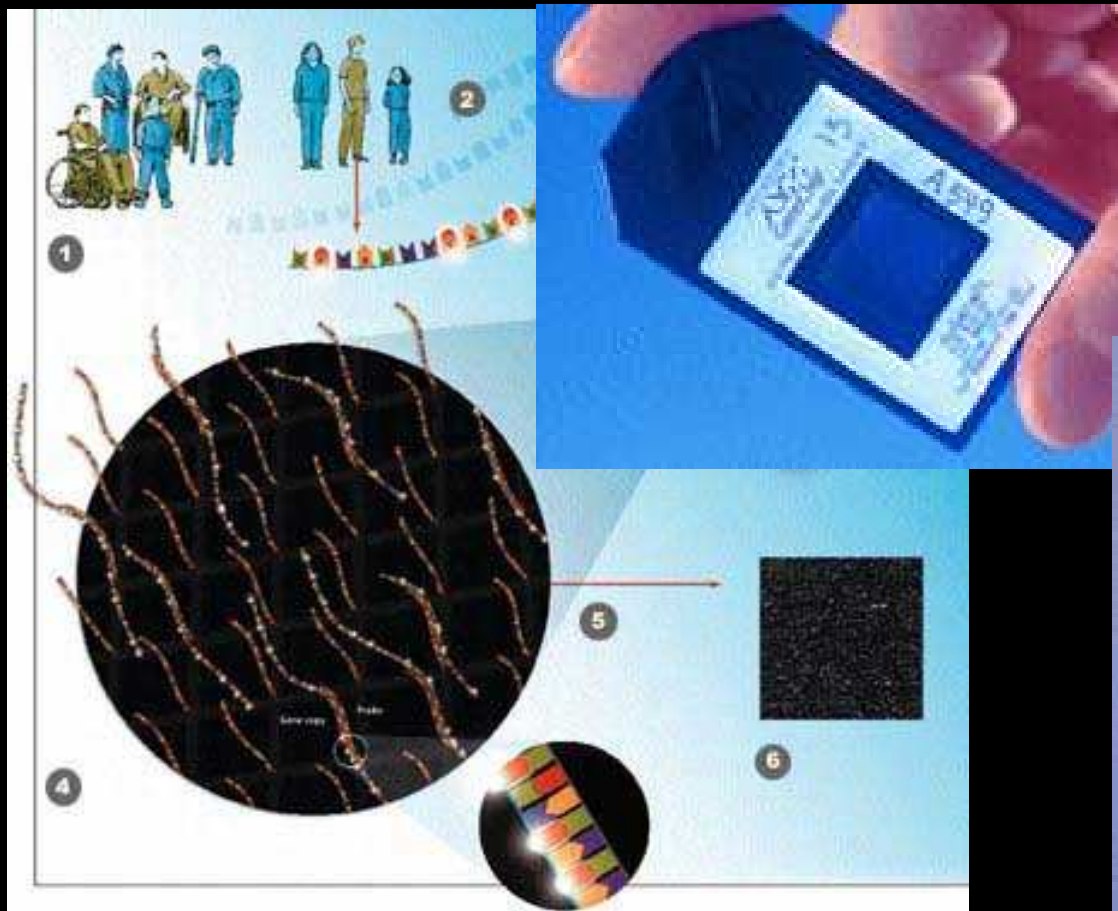
The Infotech / Biotech / Nanotech Convergence Synthetic Biology Manifestation



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Nanotech / Biotech / Infotech Convergence

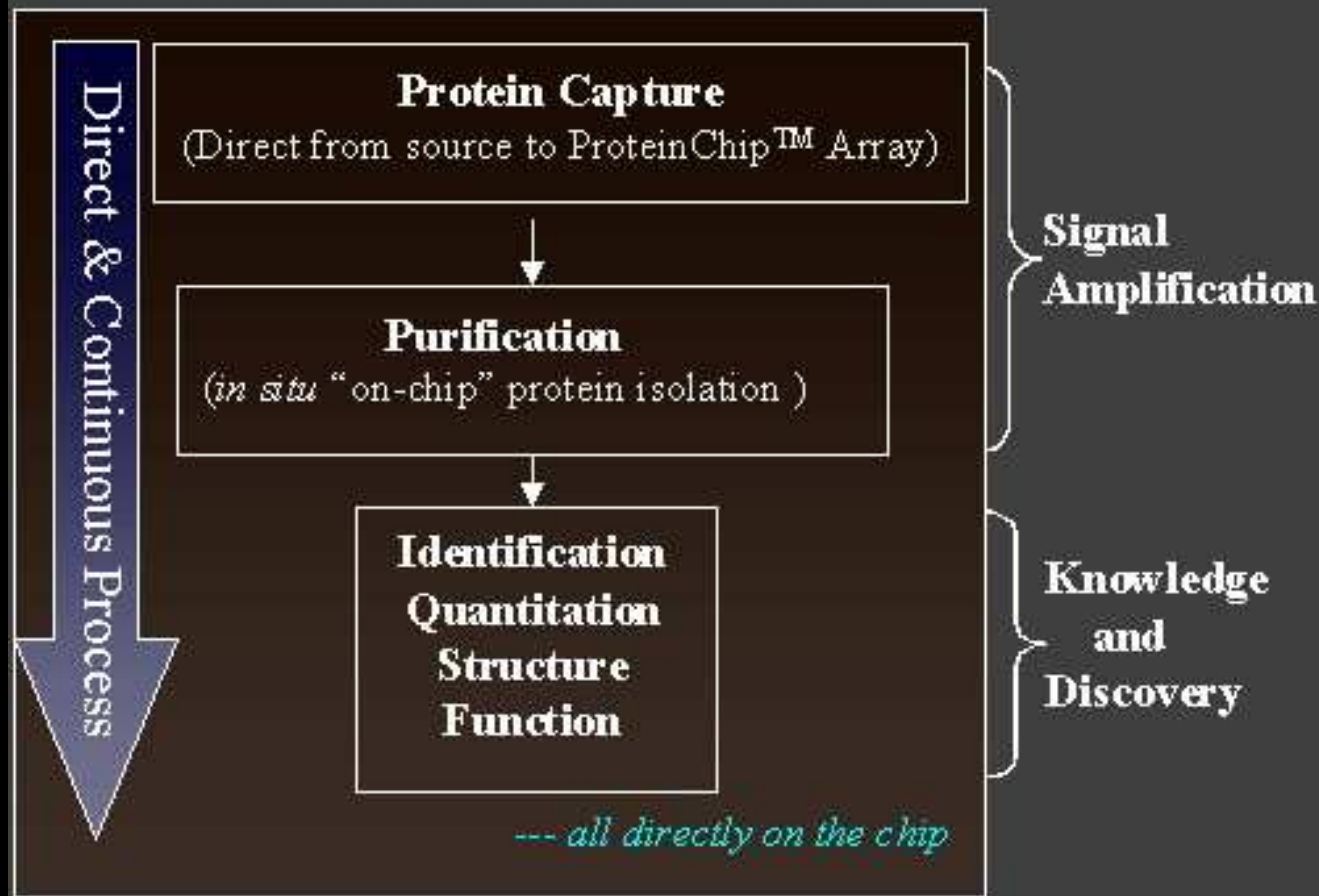
Diagnostic > Therapeutic Pipeline



Nanotech / Biotech / Infotech Convergence

Diagnostic > Therapeutic Pipeline

The SELDI™ Process

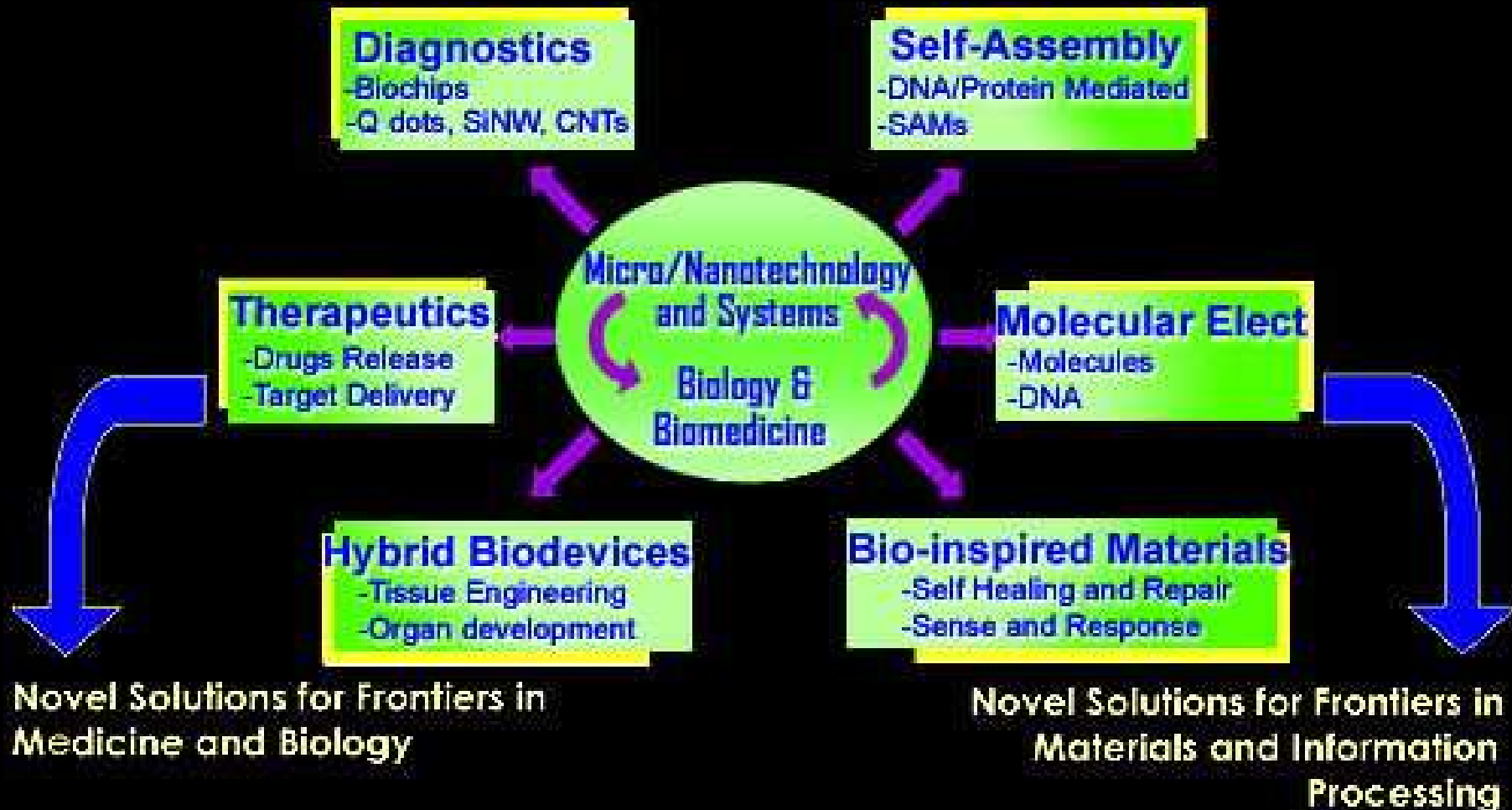


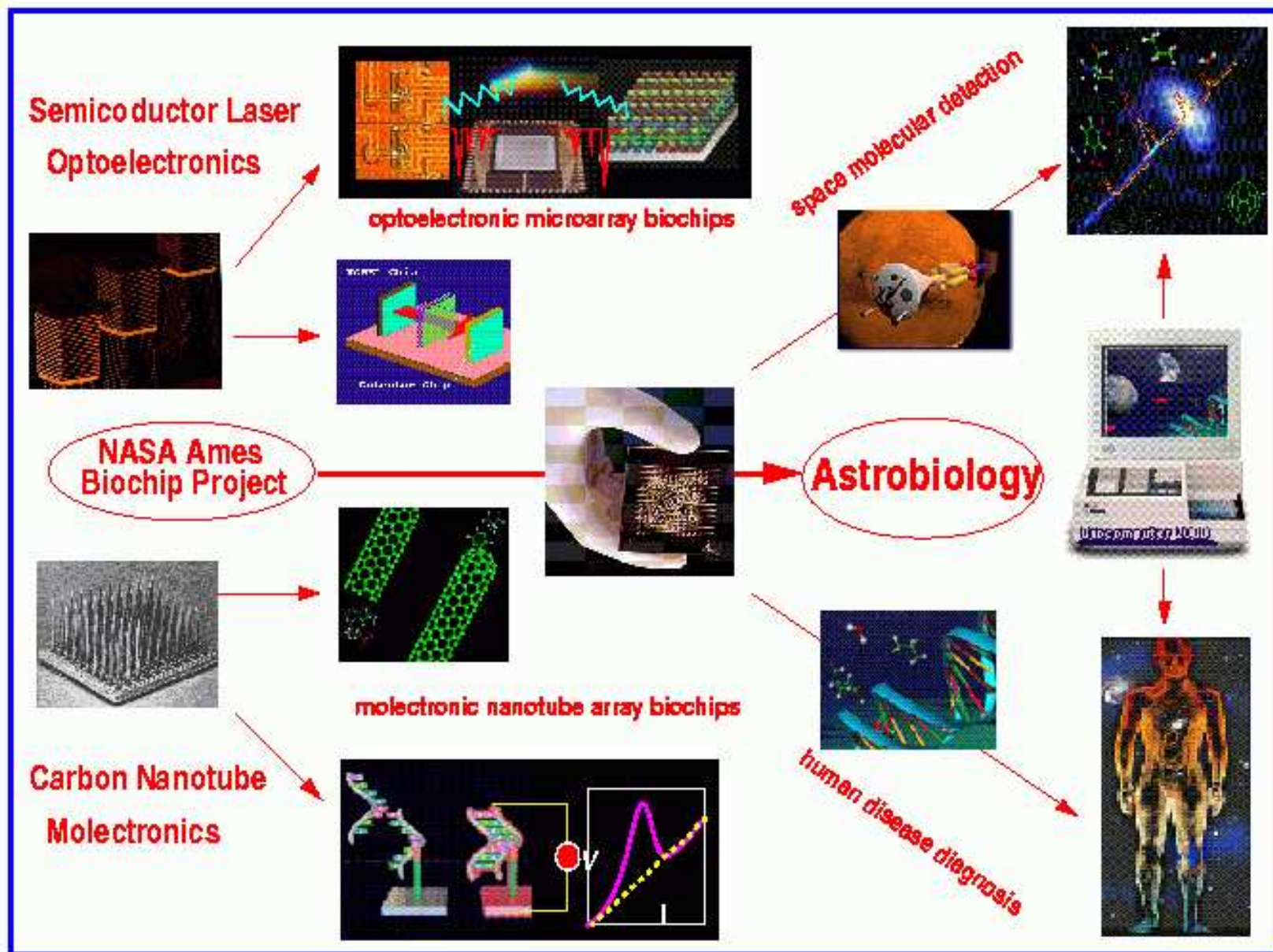
Ciphergen

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The Infotech / Biotech / Nanotech Convergence

Nanopharmaceuticals





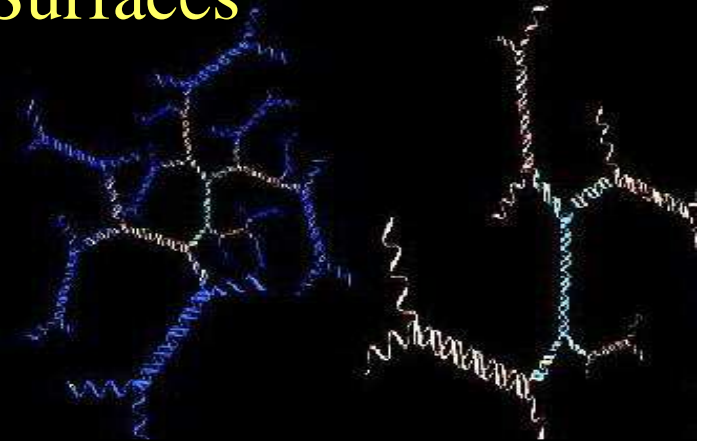
Han et al. NASA Ames Research Center, Oct. 1998

Nanomedicine - Intersection of Material Science and Medically Relevant Chemistry

- Precise targeting and penetration of intra-cellular subsystems, membranes, organelles
- Sustained dynamic physiological interaction
- Broad spectrum of potential design strategies for tightly coupled diagnostics, monitoring, and therapeutic deployment
- Nanostructured materials derived platforms > nanodevices > bio-functional deliverables

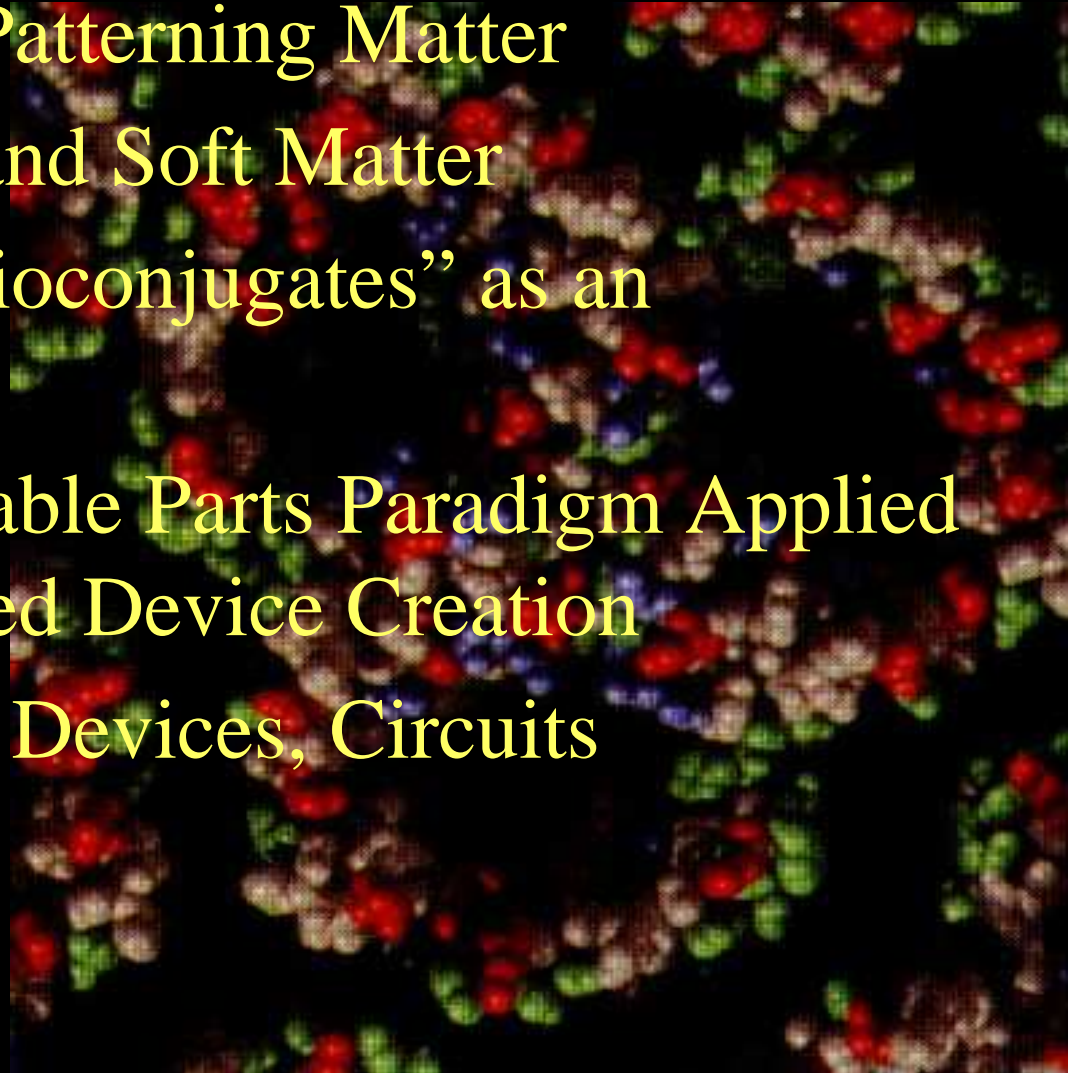
Nanotechnology Enabled Process Development Trajectories

- Enhance “Friendliness” to Novel Materials in “Traditional” Micro-litho Fab Facilities
- Integrated Biological and Non-Biological NanoStructures
- Supra-molecular Synthesis
- Integrated / Inter-related Techniques for Patterning Matter
- Chemical Handles for Attachment to Surfaces
- Utilizing Biology as a Foundry



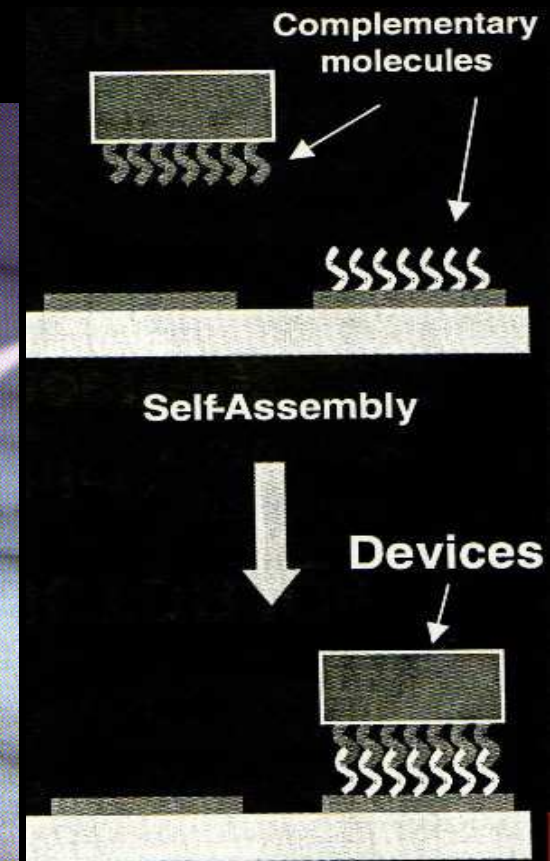
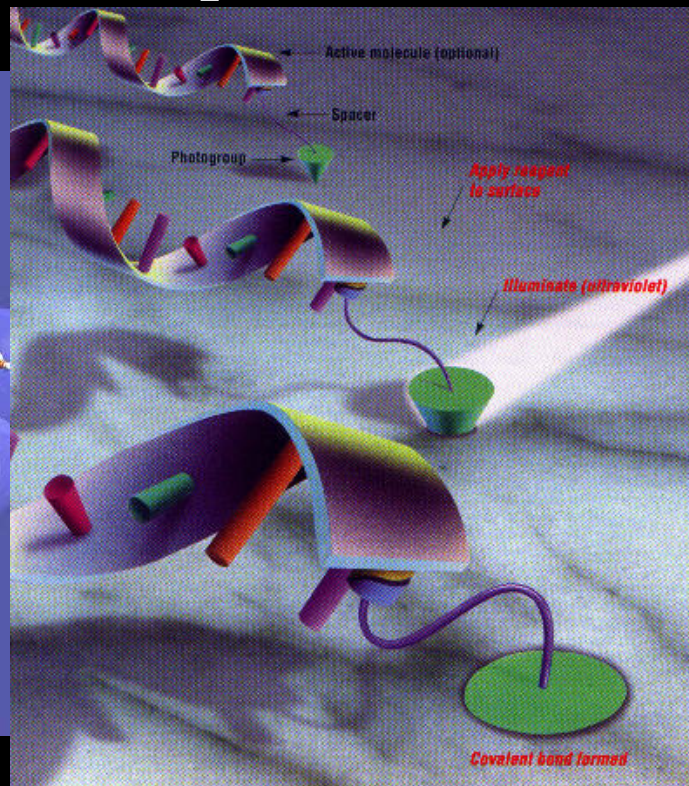
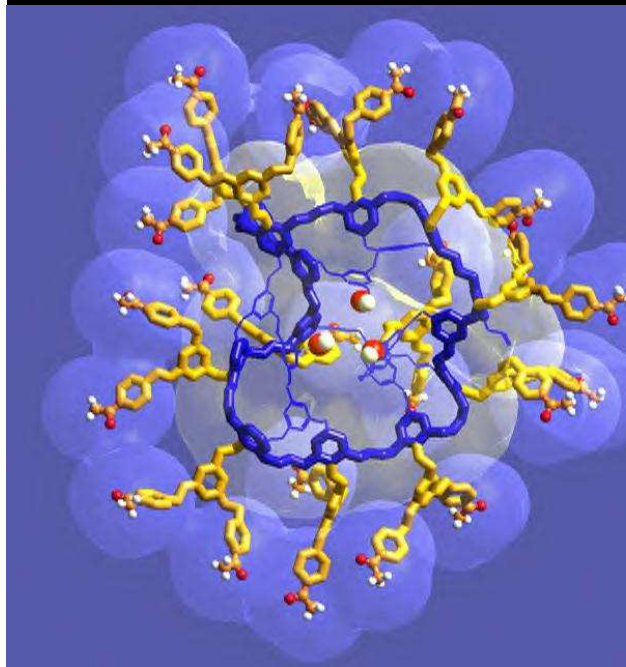
Key Nano-Industrial Infrastructure Development Indicators

- Diverse Methods for Patterning Matter
- Conjunction of Hard and Soft Matter
- Implementation of “Bioconjugates” as an Assembly System
- Whitney’s Interchangable Parts Paradigm Applied to Materials / Integrated Device Creation
- Merging of Materials, Devices, Circuits



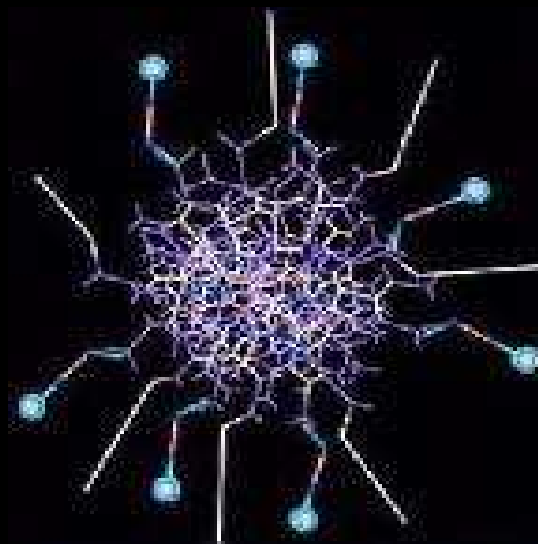
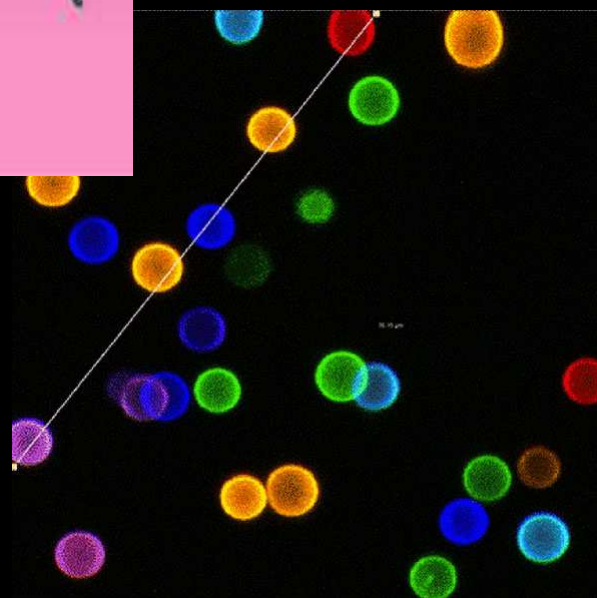
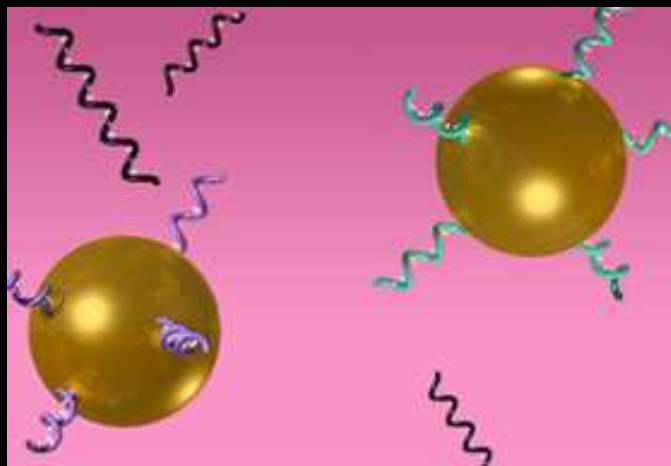
The goal is process integration

- Self Assembly / Self Organization
- Biolithography / “Soft” lithography
- Supra molecular manipulation



Complimentary Chemistries in Molecular Components

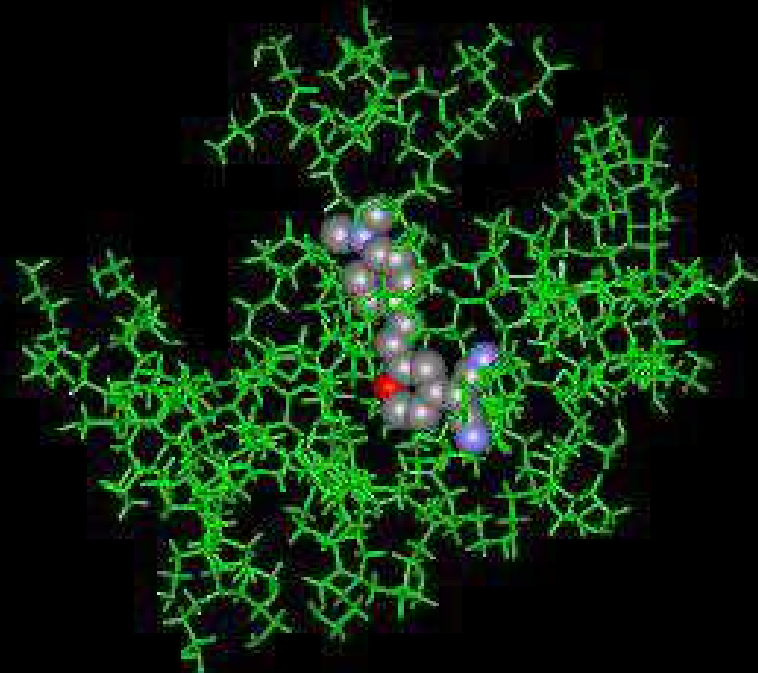
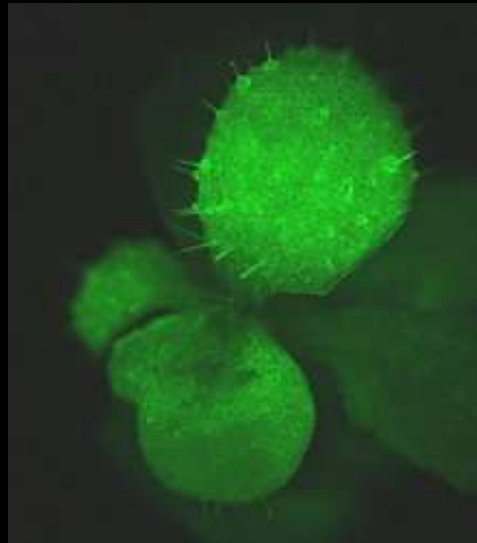
- Integration of organic and in-organic dopants with carbon nanotubes, dendrimers, various molecular structures



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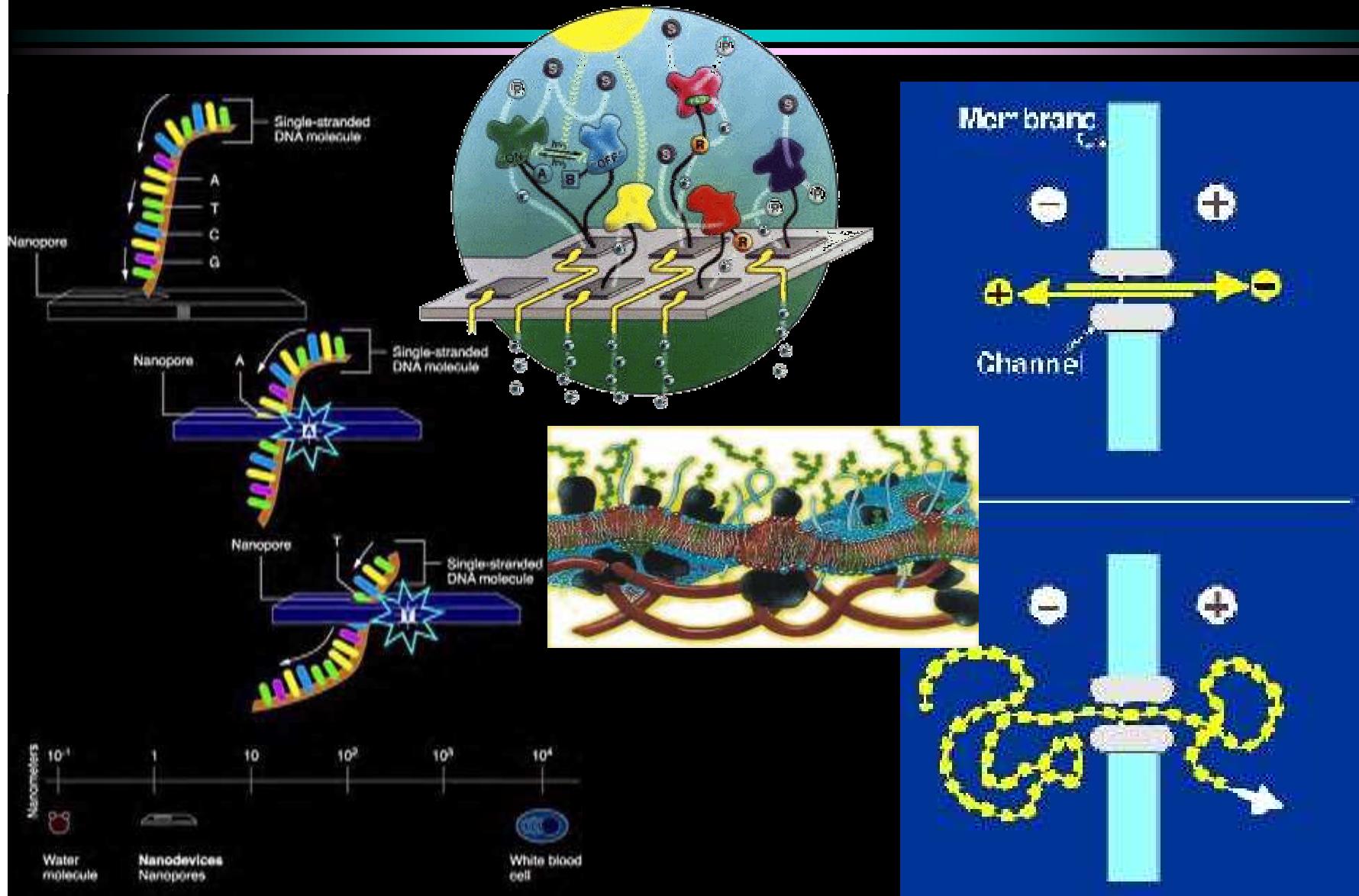
NanoDevice Platform Deliverables - Molecular Components

- Precision targeting > selective functionalities
- Prophylactic > Pathogen Inhibitor
- Synthetic systems / architectures > organelles, cells
- Enhancement
- Regulation
- Monitoring

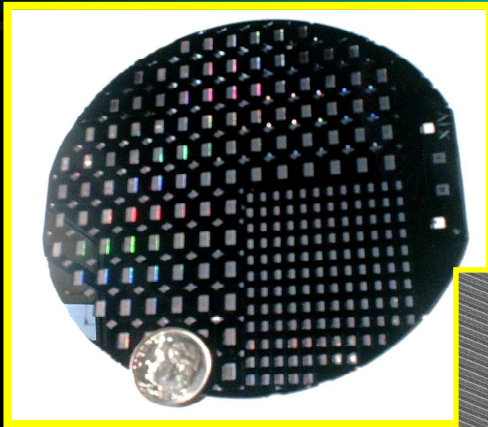


Programmable Nanoporous Materials

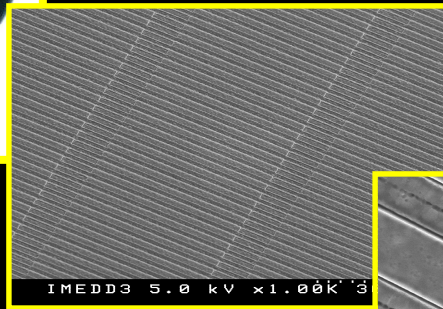
Selective / "Smart" Membranes



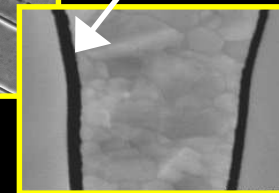
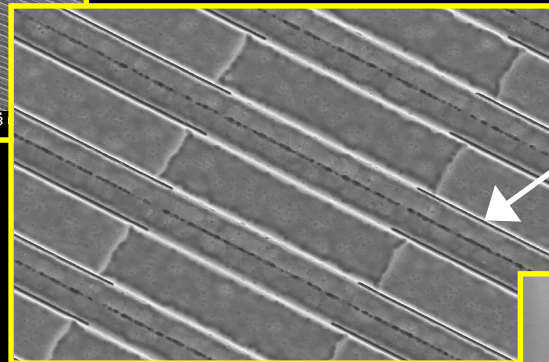
NanoGATE Membrane



4 inch wafer



Close-ups of Membrane area



Cross-section of Membrane

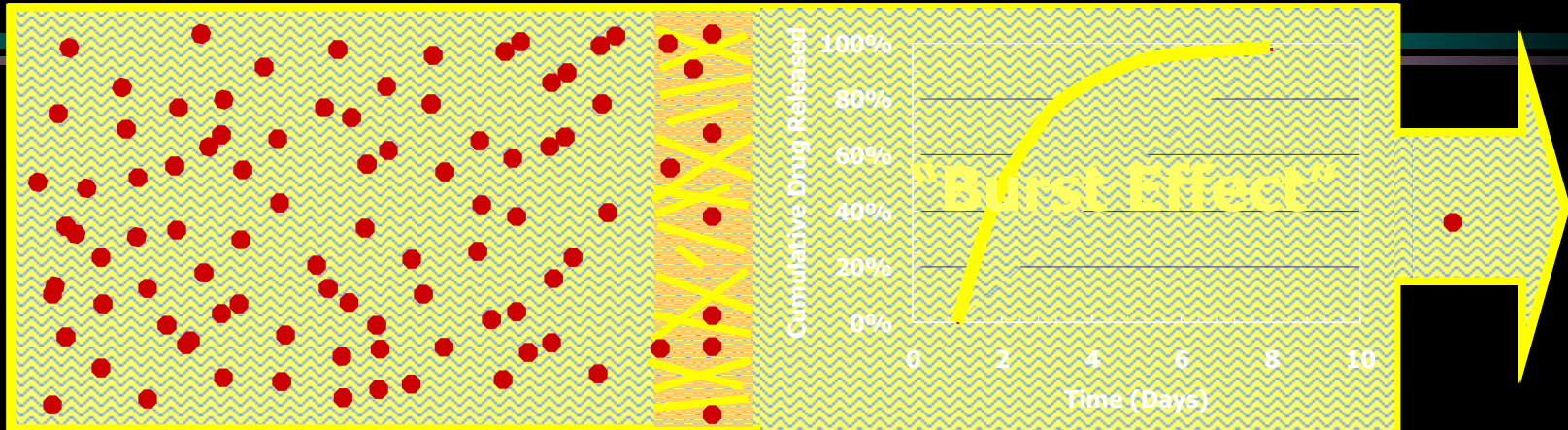
Observations

- NanoGATE openings formed by selective removal of thin layer of silicon dioxide
- Openings can be precisely controlled to be between 4 and 50 nanometers across

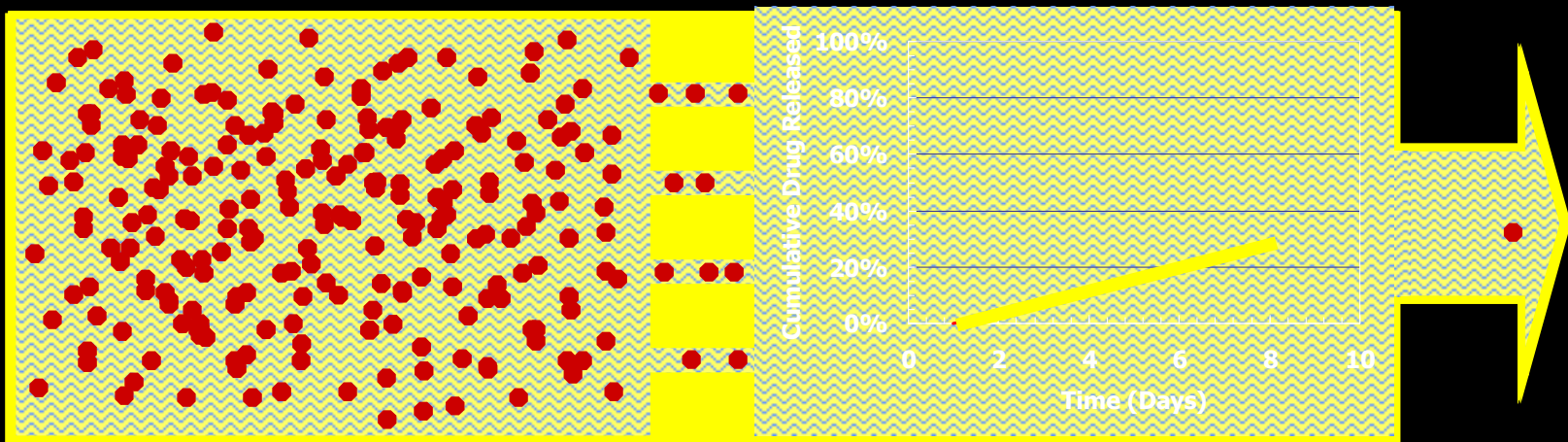
**NanoGATE openings
(20 ± 1 nm)**

NanoGATE = Molecular Gating

Diffusion of Drug through conventional membrane (Fickian release rate)

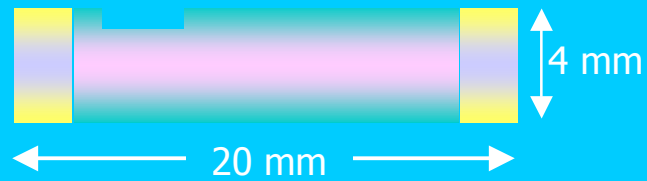


Diffusion of Drug through NanoPore membrane (Zero-order release rate)



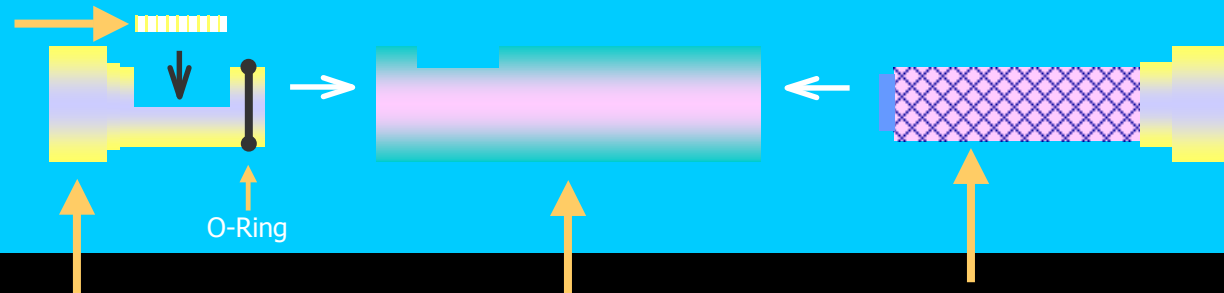
NanoGATE Prototype

Top View



Silicon membrane

Expanded View

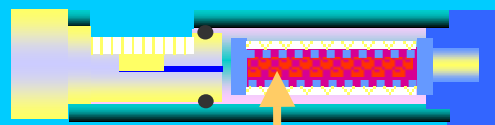


End cap and membrane support

Titanium housing

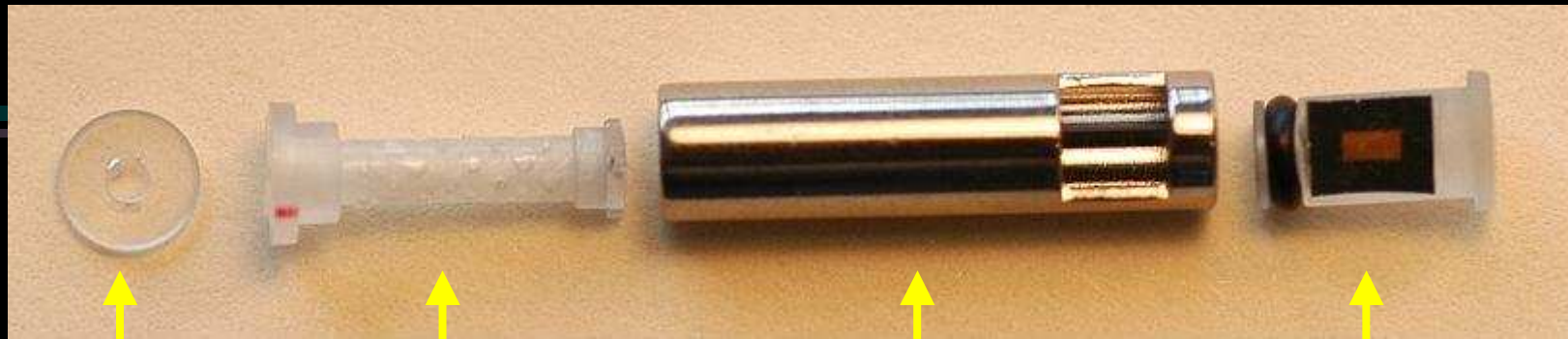
Polycarbonate membrane surrounding drug reservoir

Cross section



Formulation
(dry drug particles in non-aqueous solvent)

NanoGATE Prototype



End cap

Non-aqueous reservoir

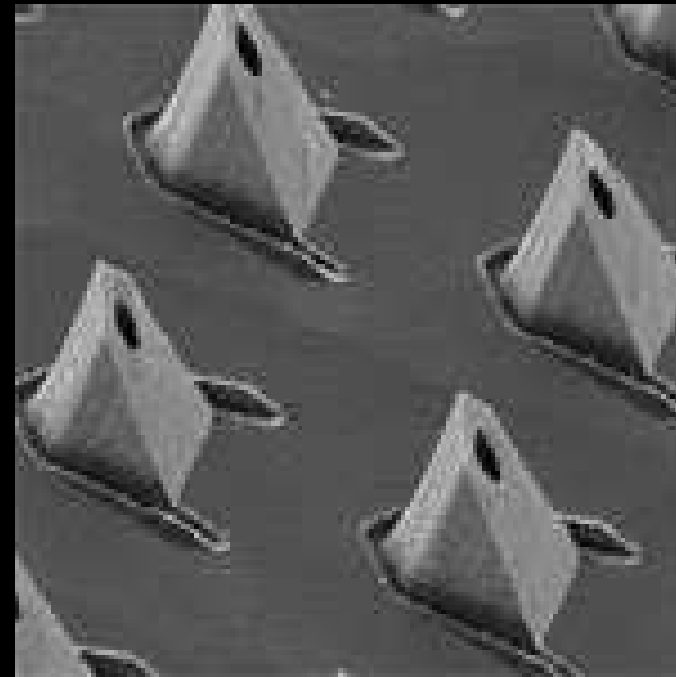
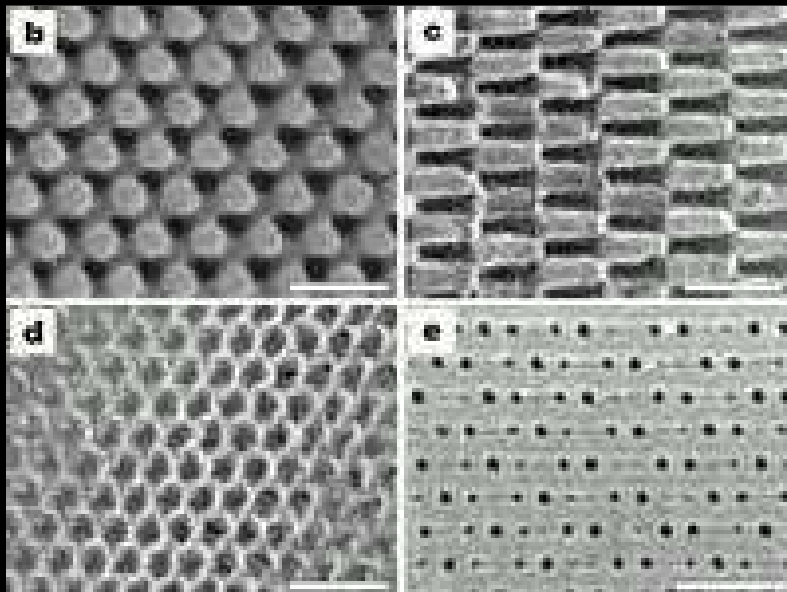
Titanium housing

Silicon membrane with support



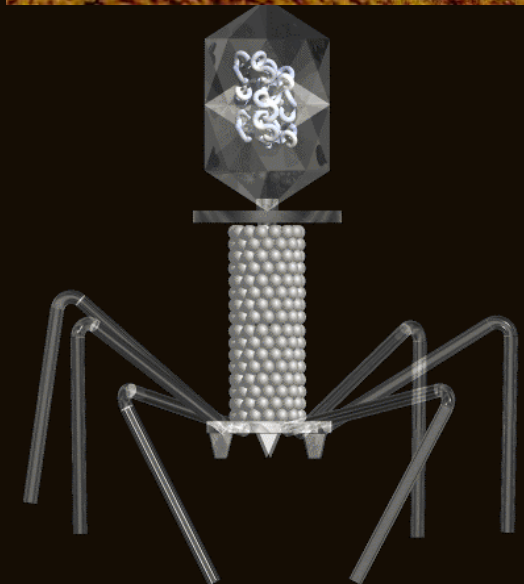
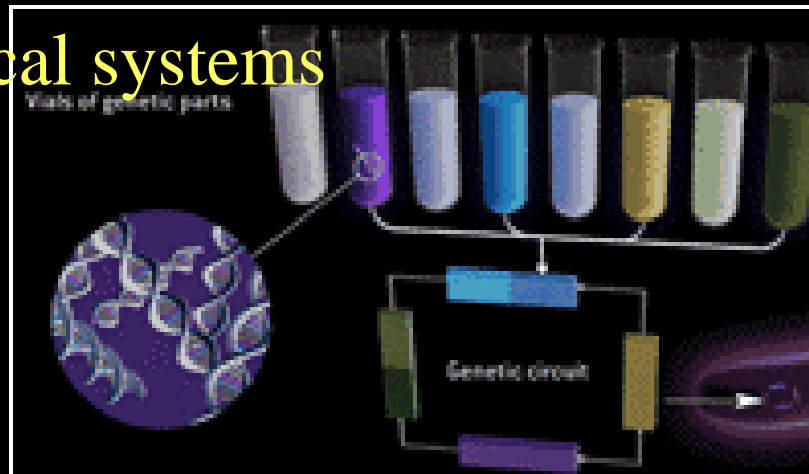
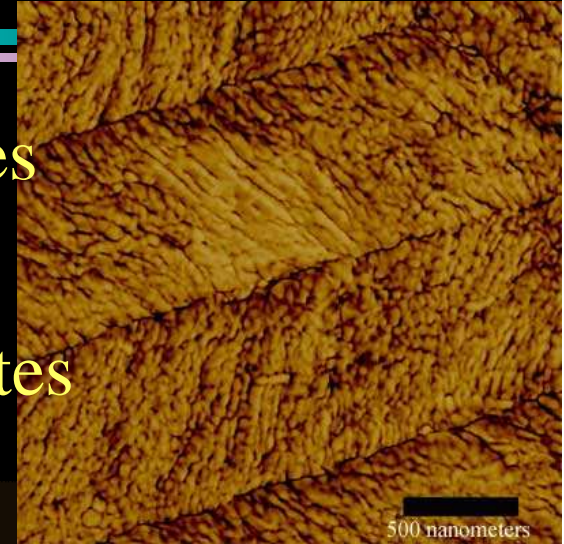
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Drug Delivery via micro / nano structured mechanisms



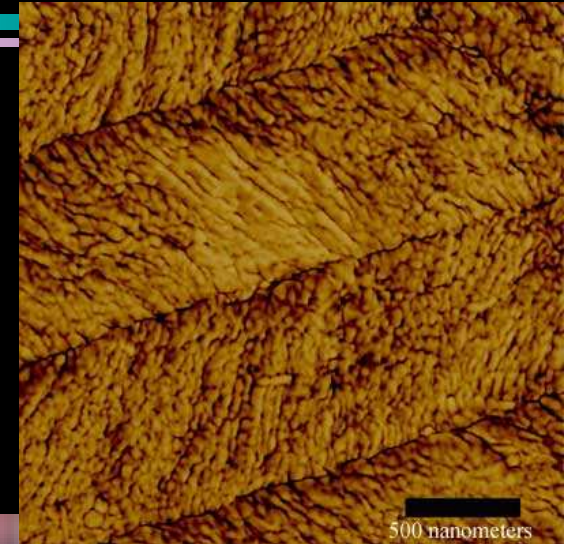
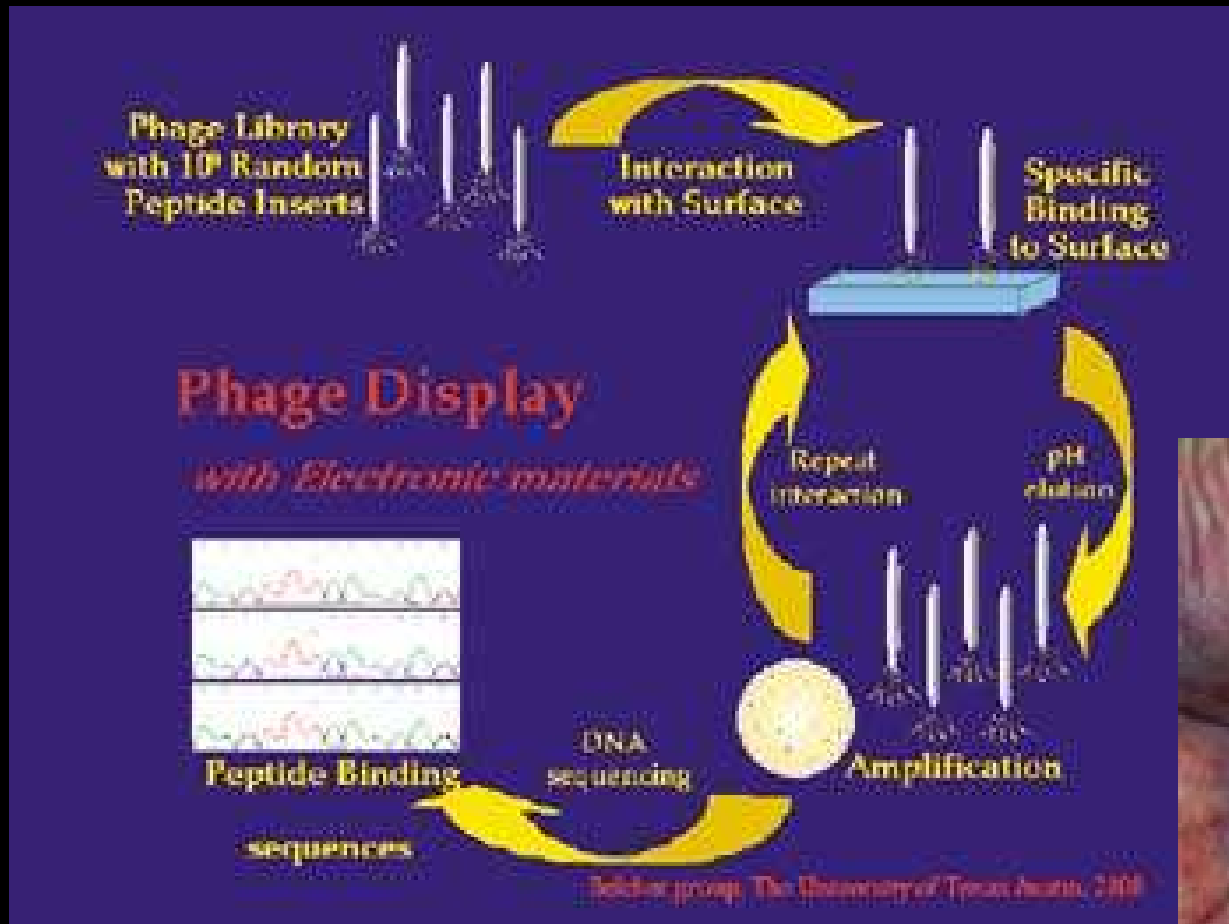
Examples of Nanofabrication Enabled by Self Assembly and Biologically Inspired Processes

- Self organizing / assembling nanostructures
- Integrated 2D and 3D structures
- Genetic “magnification” of desired attributes and affinities in biologically derived materials
- Living organisms as biofoundries and nanomechanical systems



Define Foundry

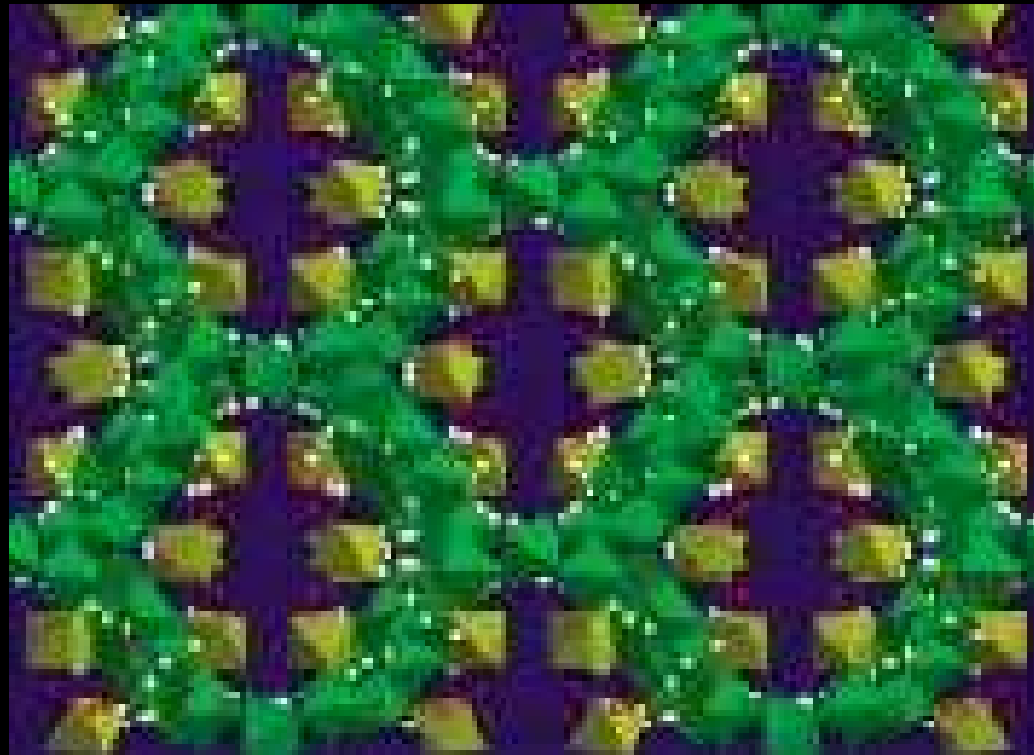
Living Systems as BioFoundries



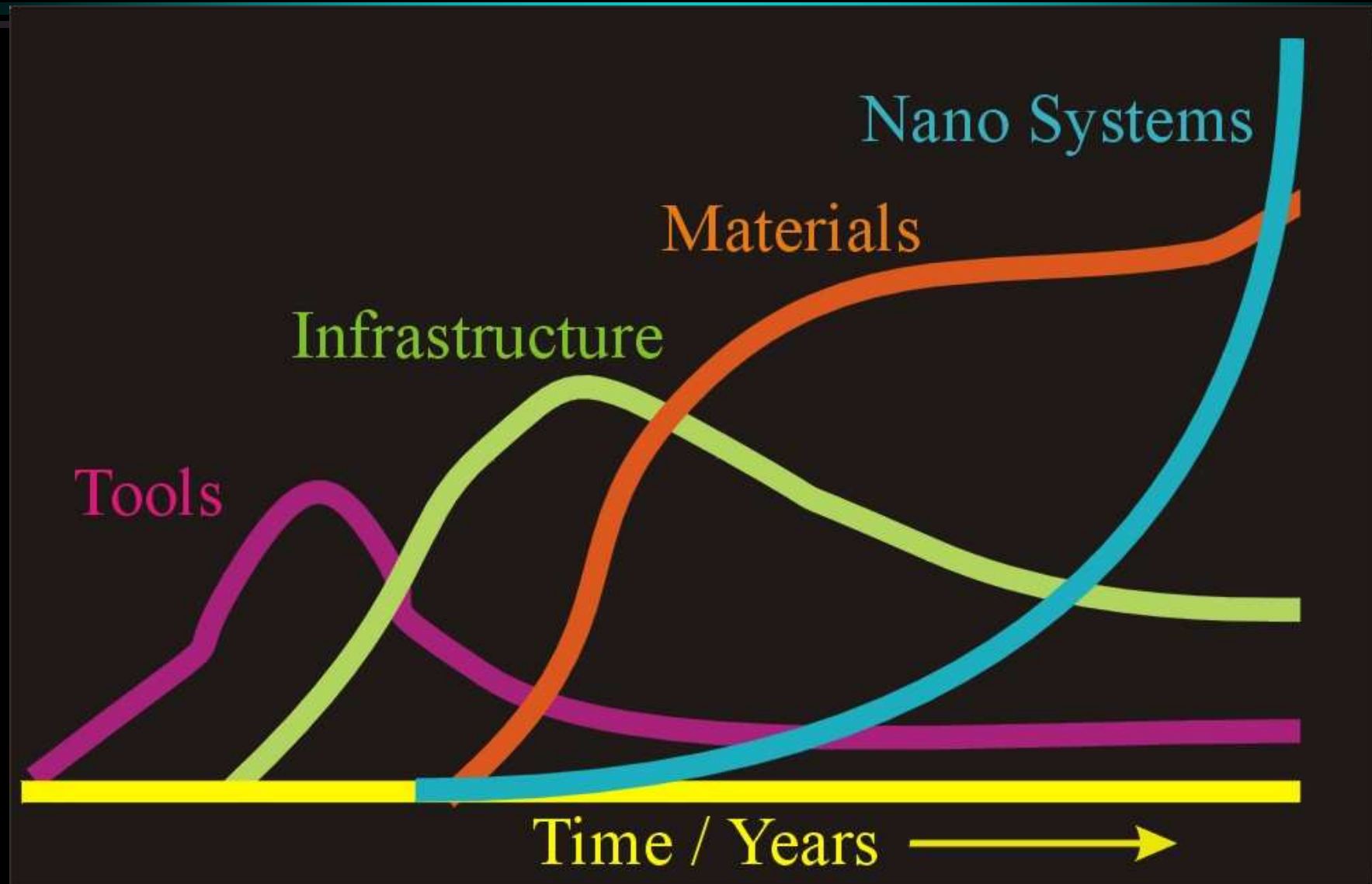
Define Foundry

Living Systems as BioFoundries

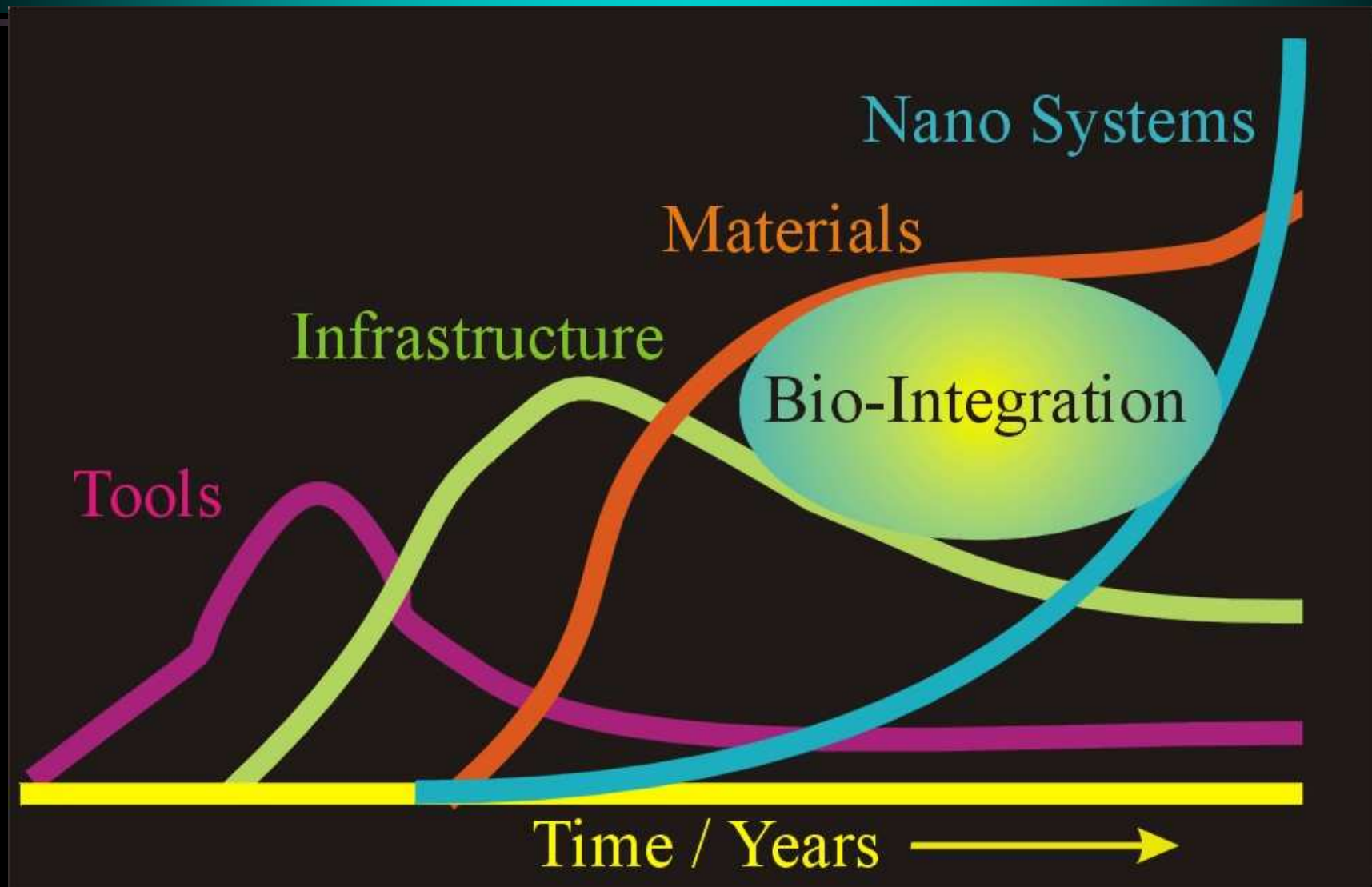
Exotic Materials
Constructs from
hybrid combinatorial
bio-conjugates and
inorganic nano-
structures



The Nano-Industrial Development Stream

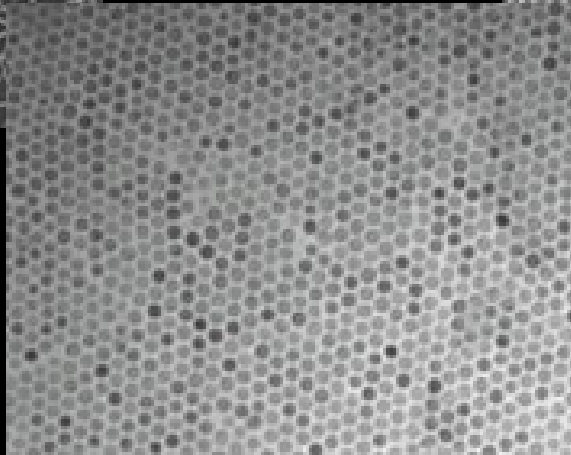
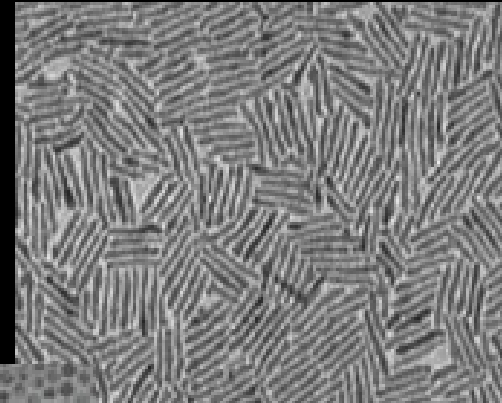
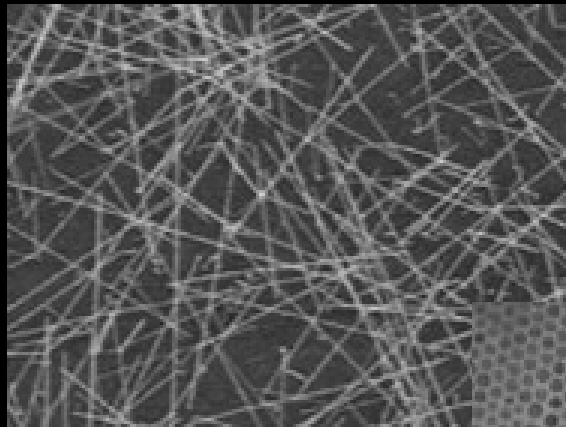


The Nano-Industrial Infrastructure Development Stream



Nanostructured Materials

- Foundry processes / fabrication techniques enabling mass production of nanostructural components
- Broad range of functionality



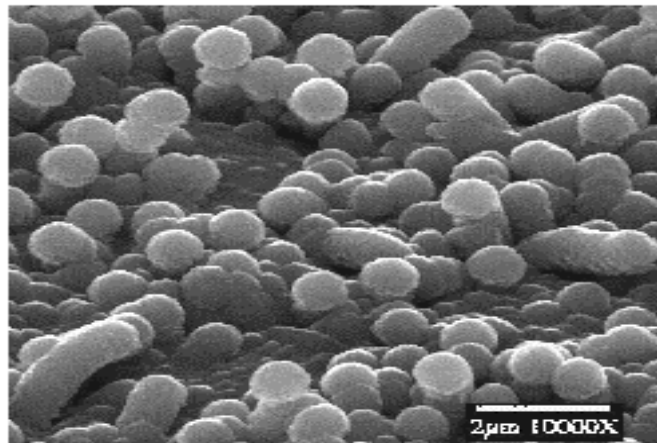
Self Assembly as a Foundry Process

Self-assembly is the most practical and realizable approach to fabricate arrays of nanodevices with the sub-100nm size features in short-term (the conventional lithographic methods of microsystem processing offer very limited control over the fabrication on the sub-100 nm scale)

Spontaneous self-assembly



This approach relies on structural disorder at the interface between the two materials with different physical properties (heteroepitaxy, fluctuations of the dopant concentration, etc.)



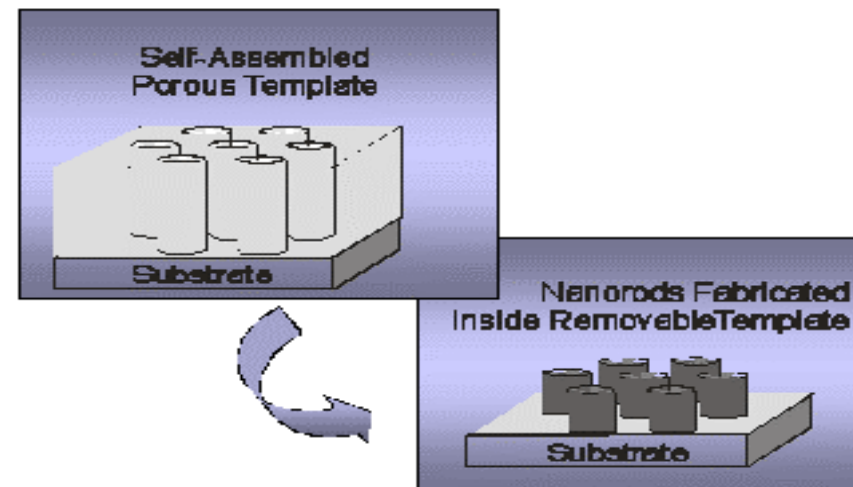
Self-assembled Si nanowires grown by magnetron sputtering

(E.A. Gulians and W.A. Anderson, "A Novel Method of Structure Control in Si Thin Film Technology", 197th Meeting of The Electrochemical Society Toronto, ON, May 2000)

Controllable self-assembly

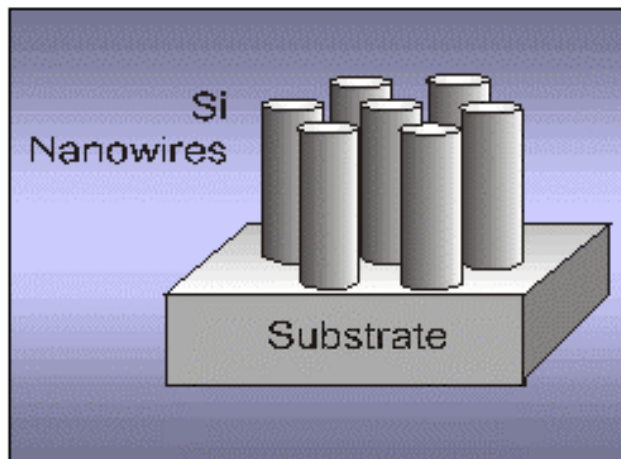


Involves self-assembly of the tools for fabrication of nanostructures and nanodevices, such as masks or templates.

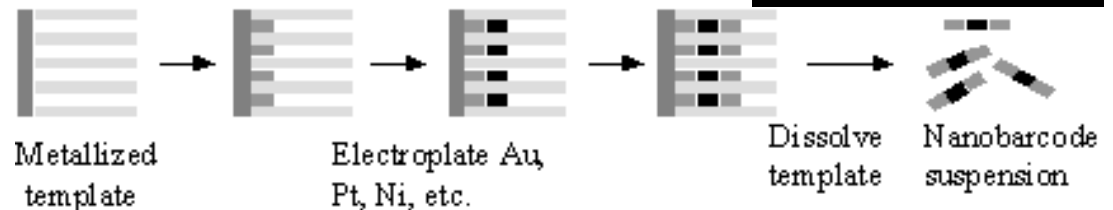
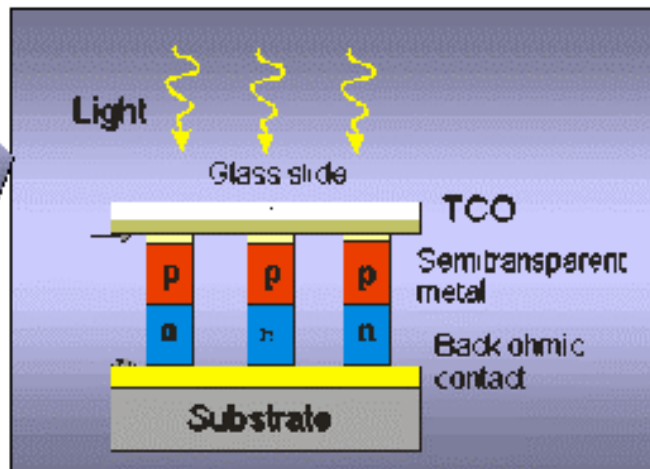


Periodic Nanostructures

Some of the potential applications of periodic nanostructures are:



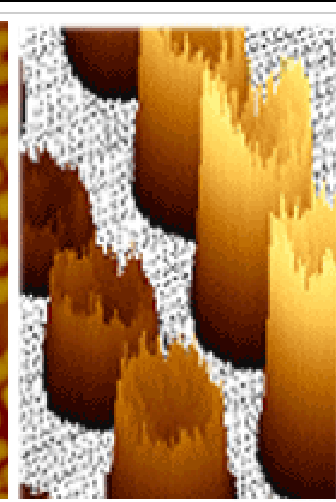
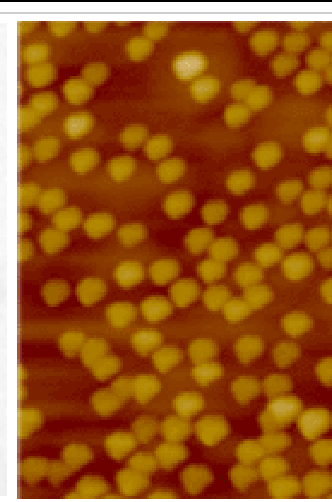
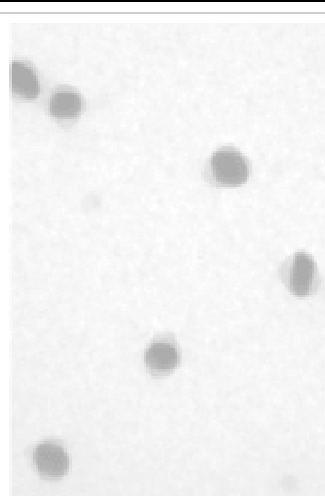
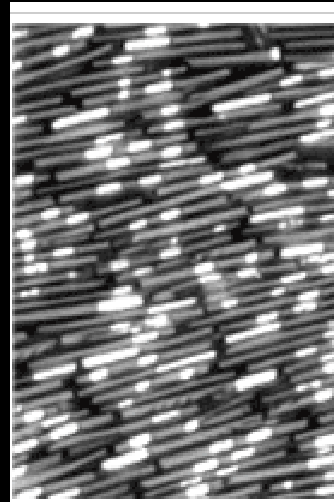
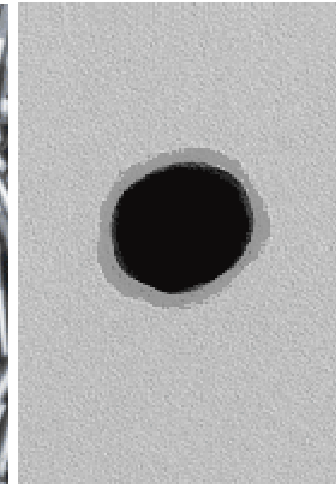
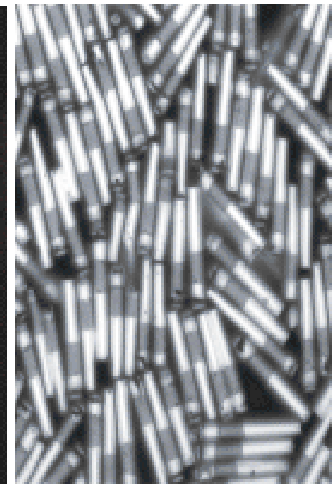
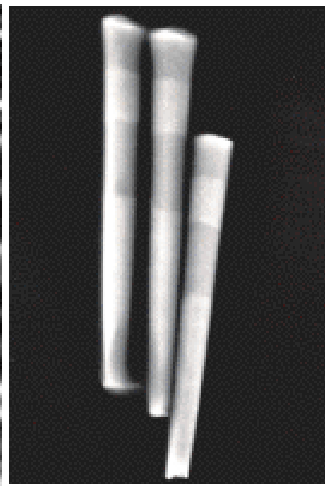
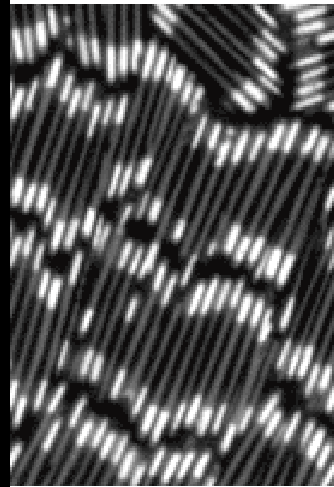
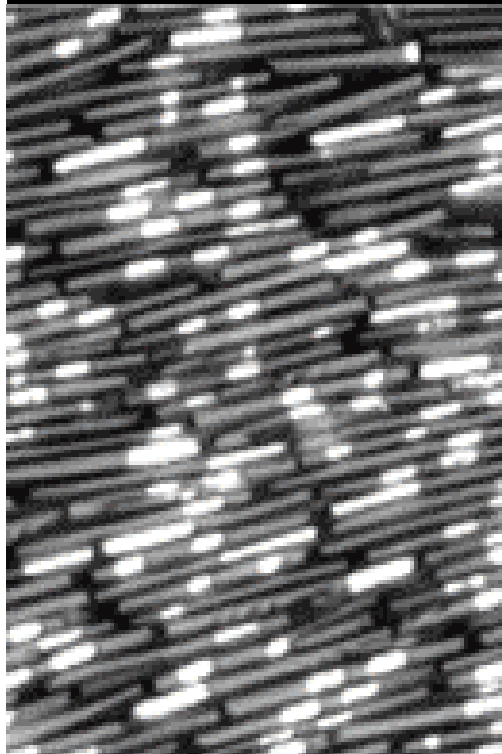
- Quantum effect dots
- Resonant tunneling diodes
- Single-domain/bit magnetic storage media
- Single electron transistors (SETs)
- Light-emitting diodes (LEDs)
- Photodetectors
- Quantum well optoelectronic devices
- Quantum cellular automata
- High-density memory



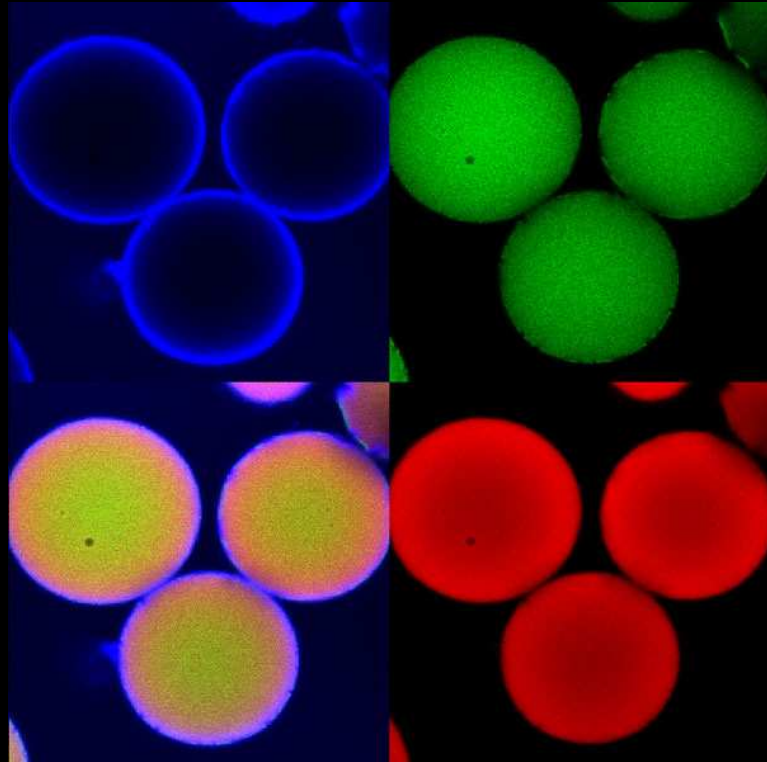
Schematic of a Si photodetector array fabricated on periodic Si nanowires

Periodic Nanostructures

NanoPlex
Technologies



Spherical Periodic Nanostructures



The color of the the light emitted by the dots is dictated by their size.



1.2 nm



1.5 nm



2.1 nm



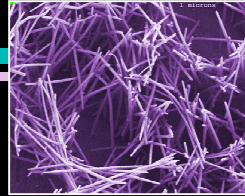
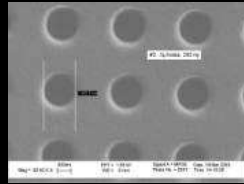
GE Nanotechnology Platforms

NanoTubes/NanoRods

SW/MWNT, Pt, Ni, MoC...

Application Areas

- Sensors...

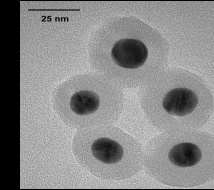
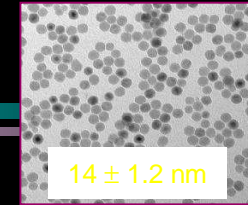


NanoParticles

Fe_2O_3 , Gd_2O_3 , Au...

Application Areas

- Molecular Imaging
- BioSensors...

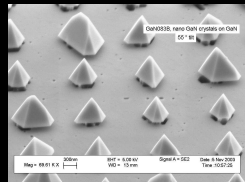
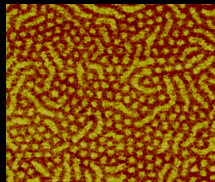


NanoHybrids

Block copolymers, GaN...

Application Areas

- Lighting – white LED...



NanoCeramics

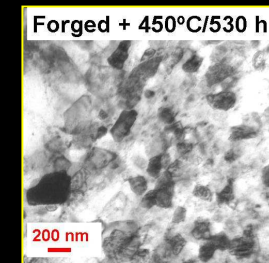
Application Areas

- Optical materials
- Structural ceramics...

NanoMetallics

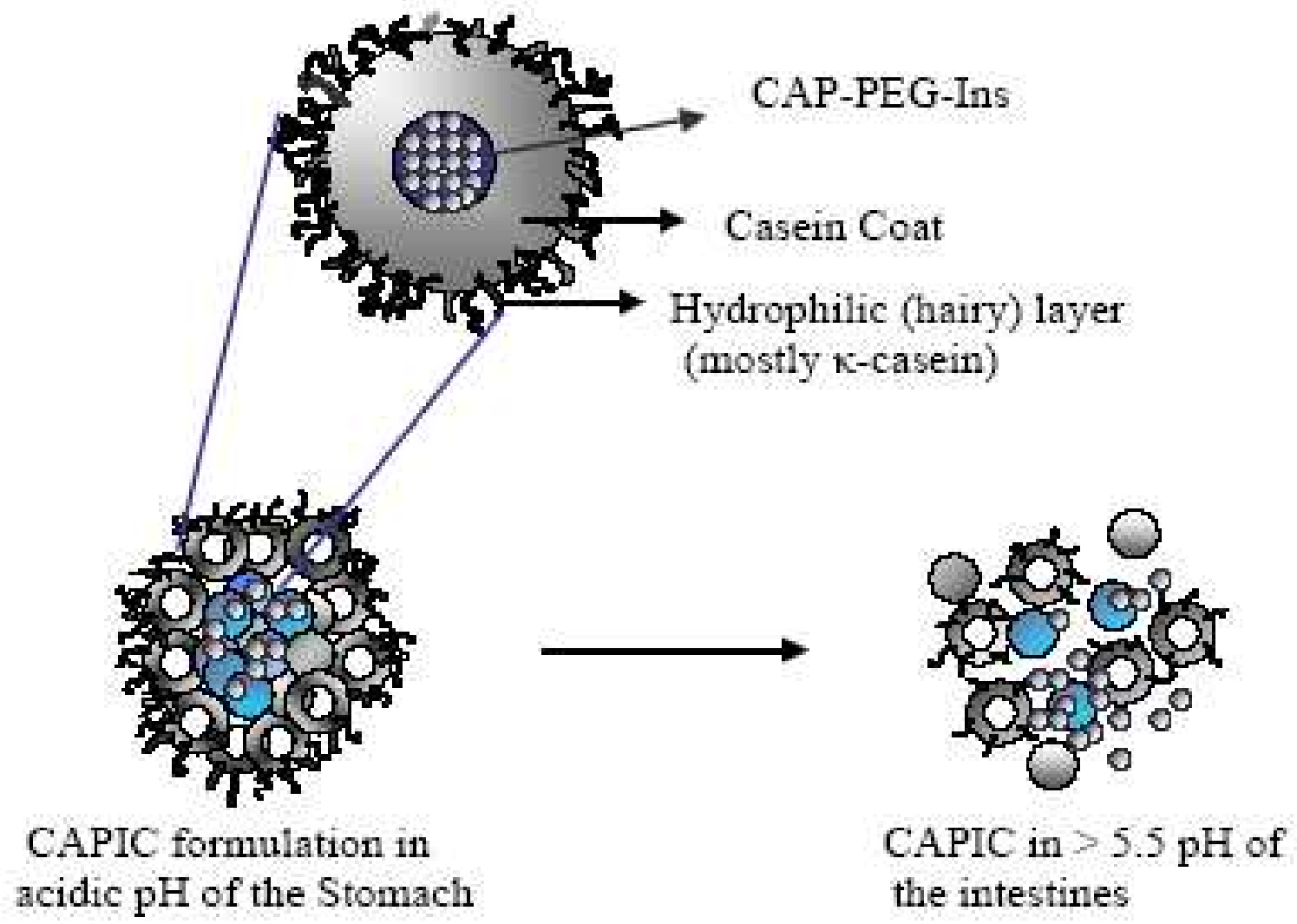
Application Areas

- High strength materials
- Thermal barriers...

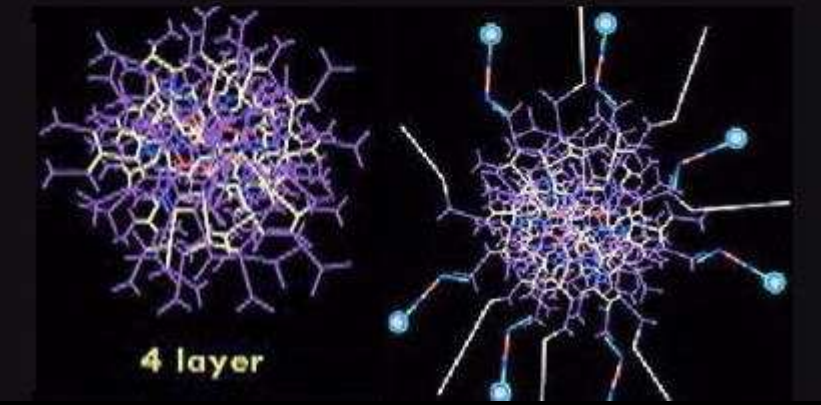
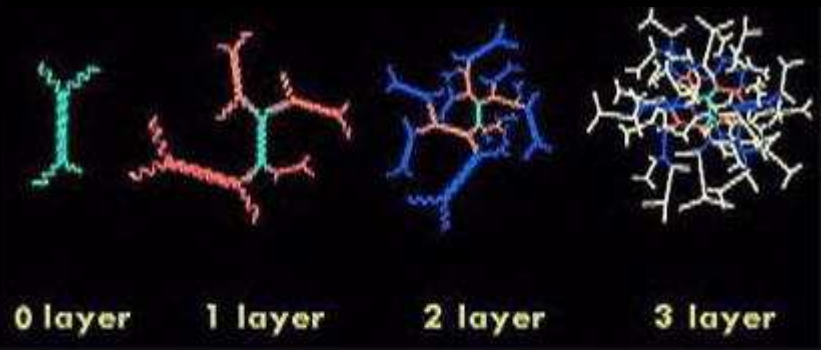
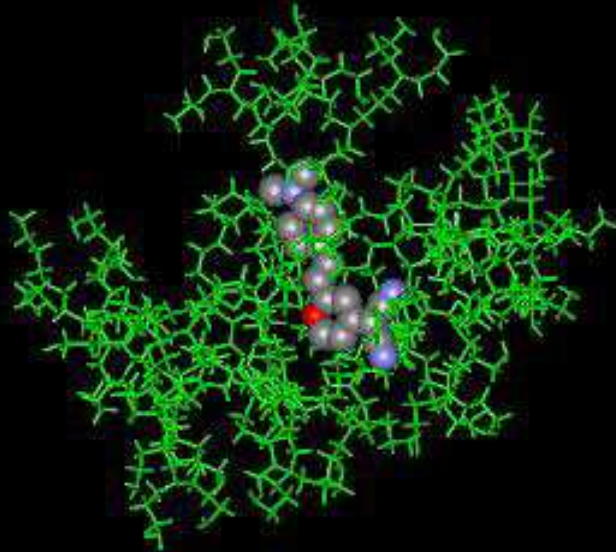
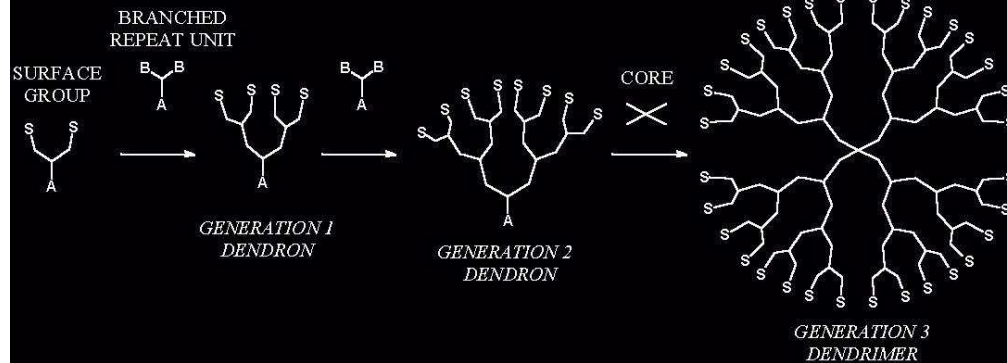
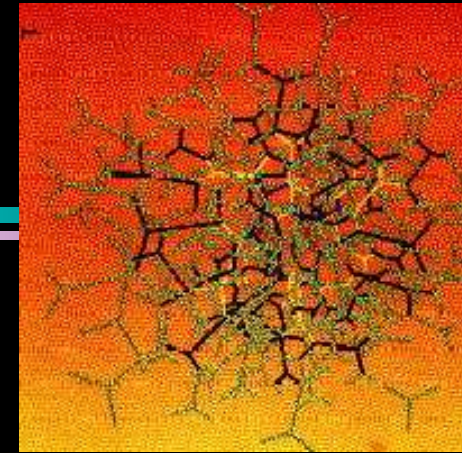


broad range of nanomaterials

BioSante – Casein coated CAP-PEG-Ins (biodegradable calcium phosphate insulin) particles for potential oral delivery



Dendrimers – molecular delivery vehicle

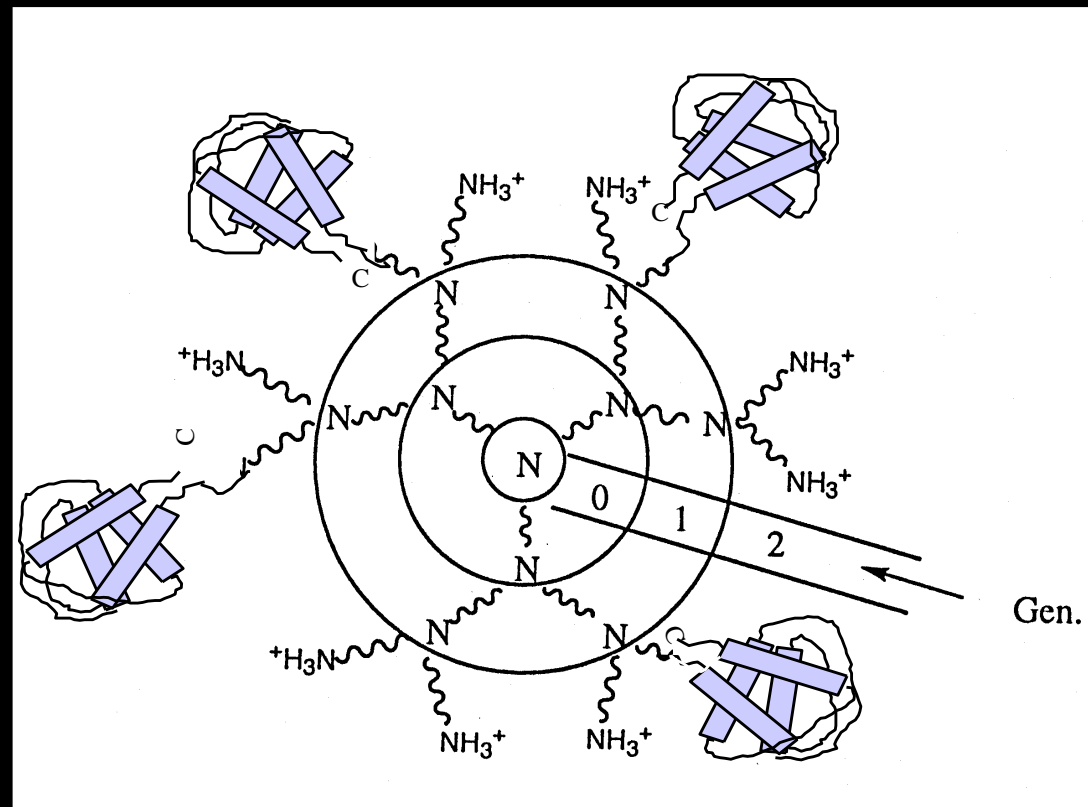


Immune responses to nanomaterials ...

One approach:
isofunctional
device variants
tailored to
individuals

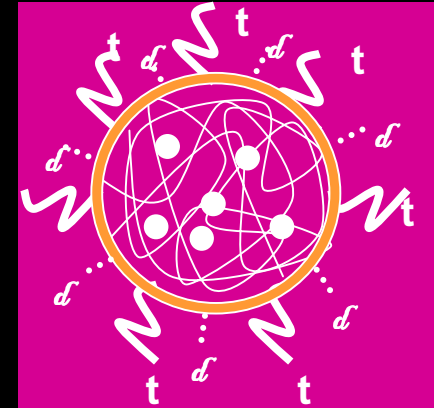
one device
becomes many...
What if it contained
multiple proteins?

Lee *et al.* 2001. *Biomedical Microdevices*. **3**: 51-57.
Lee *et al.* 2004. *Biomedical Microdevices*, *in press*



How many possible protein components of nanodevices are there?

- At least 25,000 genes in humans¹
- At least 100,000 proteins¹
- $>3 \times 10^9$ living species described to date
- Exponential numbers of engineered variants of each protein are possible



1. Southan. 2004. *Proteomics* 4: , 1712-1726

2. Edwards et al. 2000. *Science* (2000 Sep 29), 289: 2312-4.

Is there a reason for fungible protein components of nanodevices?

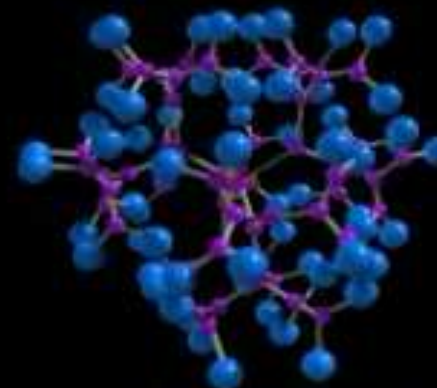
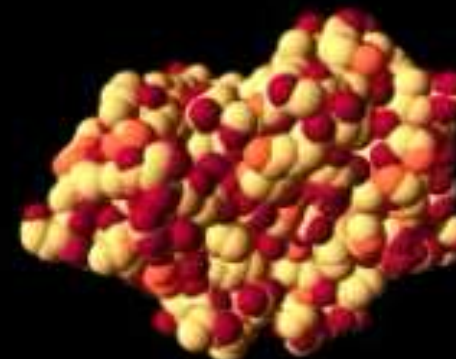
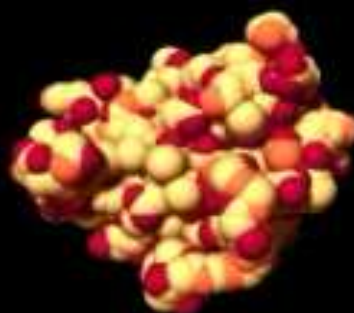
Protein Size Mimicry

10 nanometers

Hemoglobin

Cytochrome

Insulin



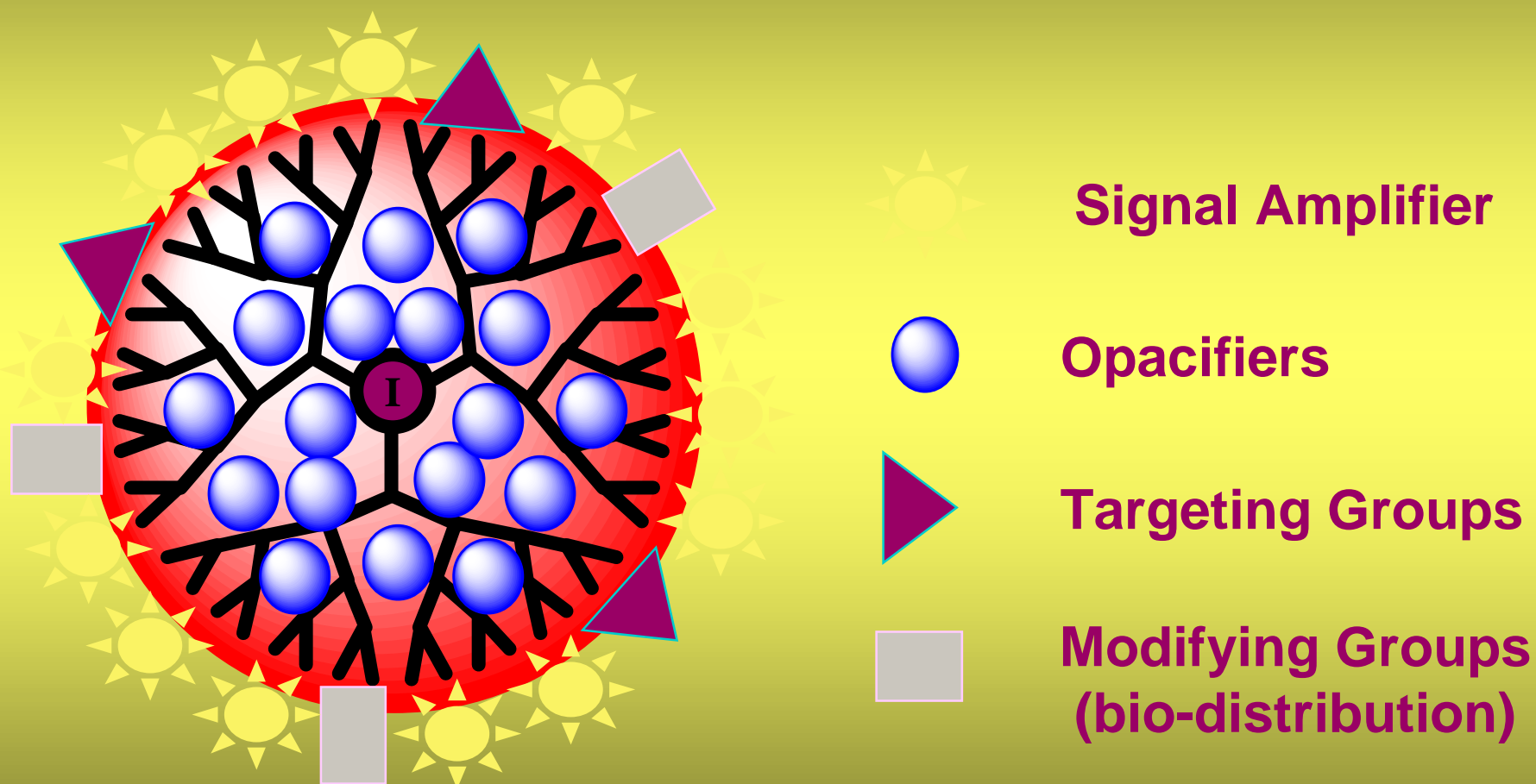
Generation 3
3 nanometers

Generation 4
4 nanometers

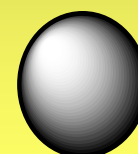
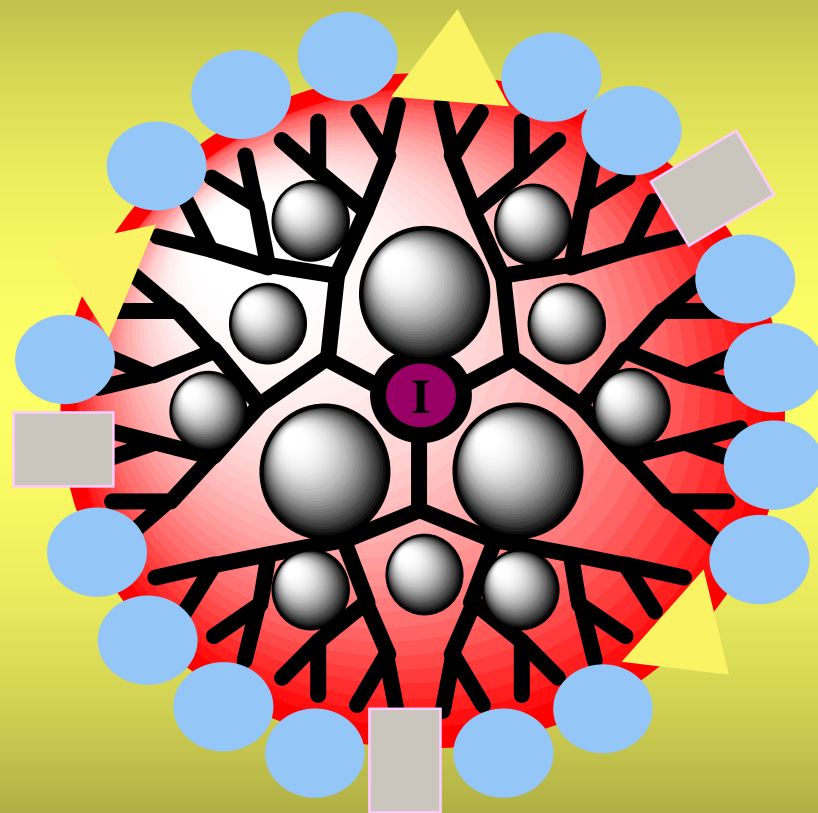
Generation 5
5 nanometers

0

Dendrimers as Nano-Diagnostics



Dendrimers as Nano-Delivery Containers



Active Pharma



Delivery Control Groups

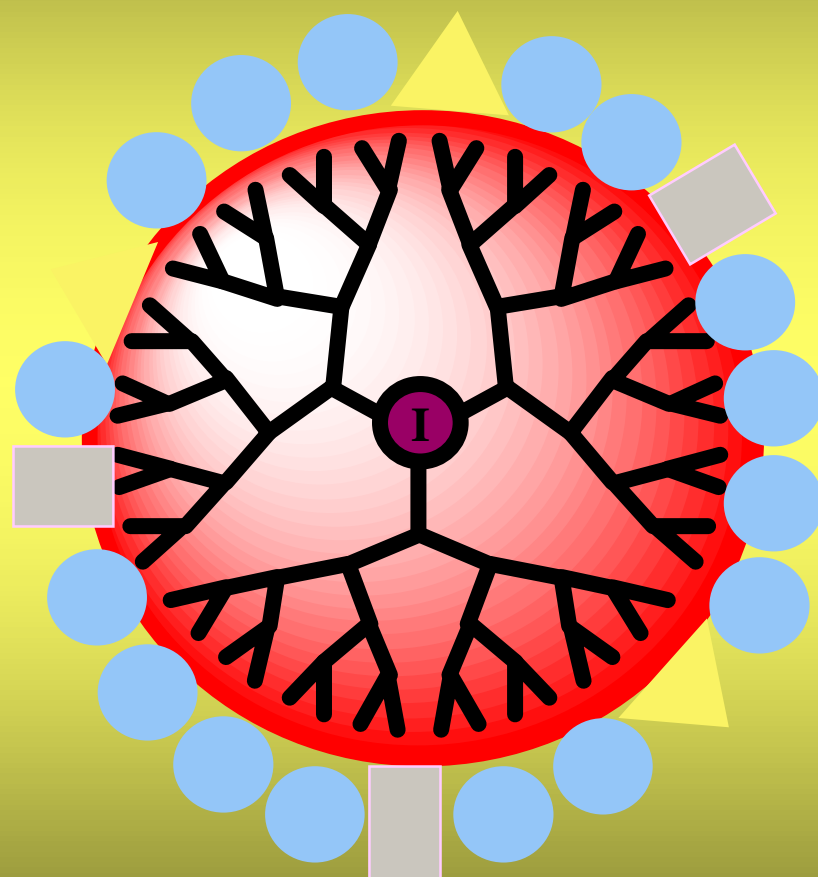


Targeting Groups



**Modifying Groups
(bio-distribution)**

Dendrimers as Nano-Drugs



Active Groups

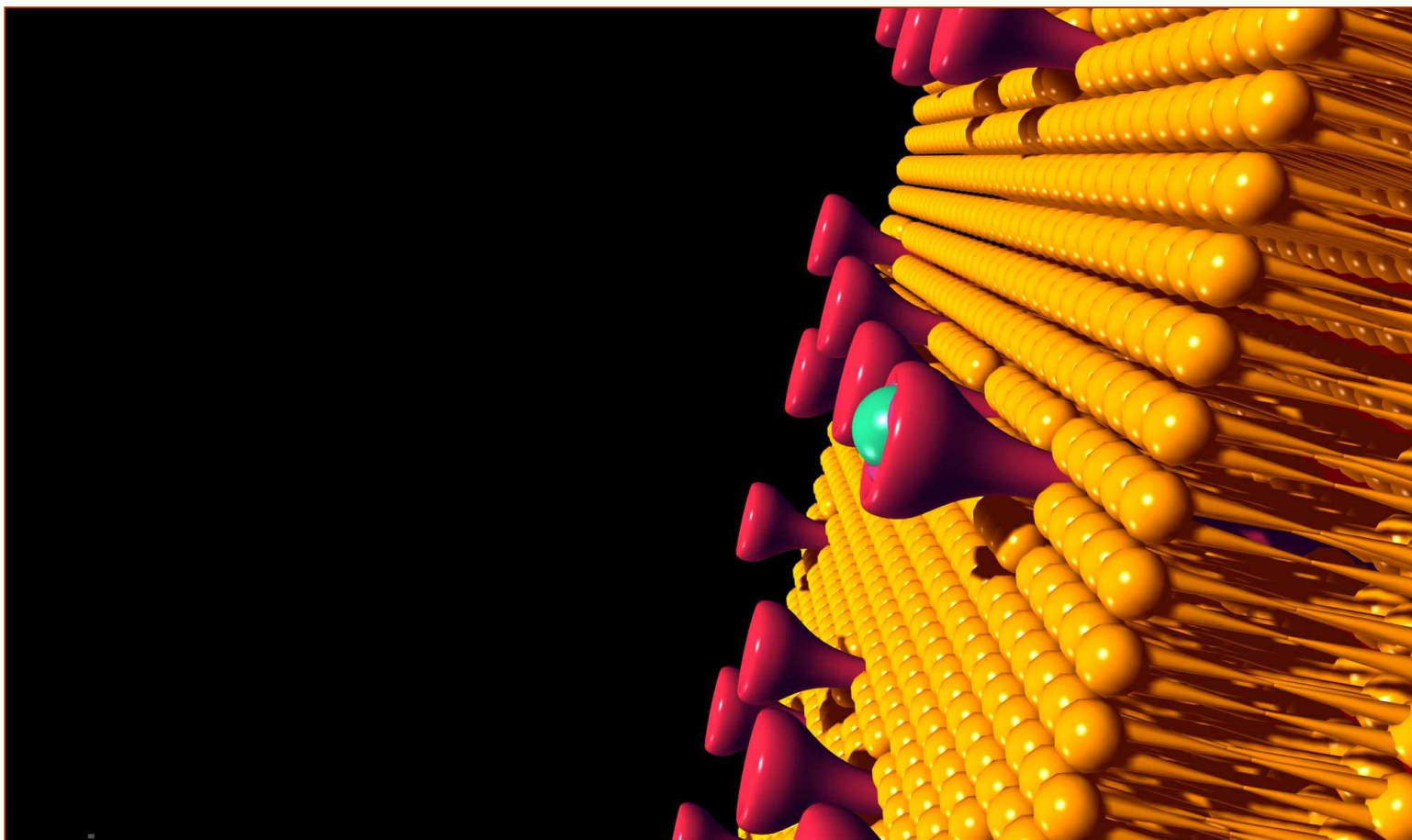


Targeting Groups



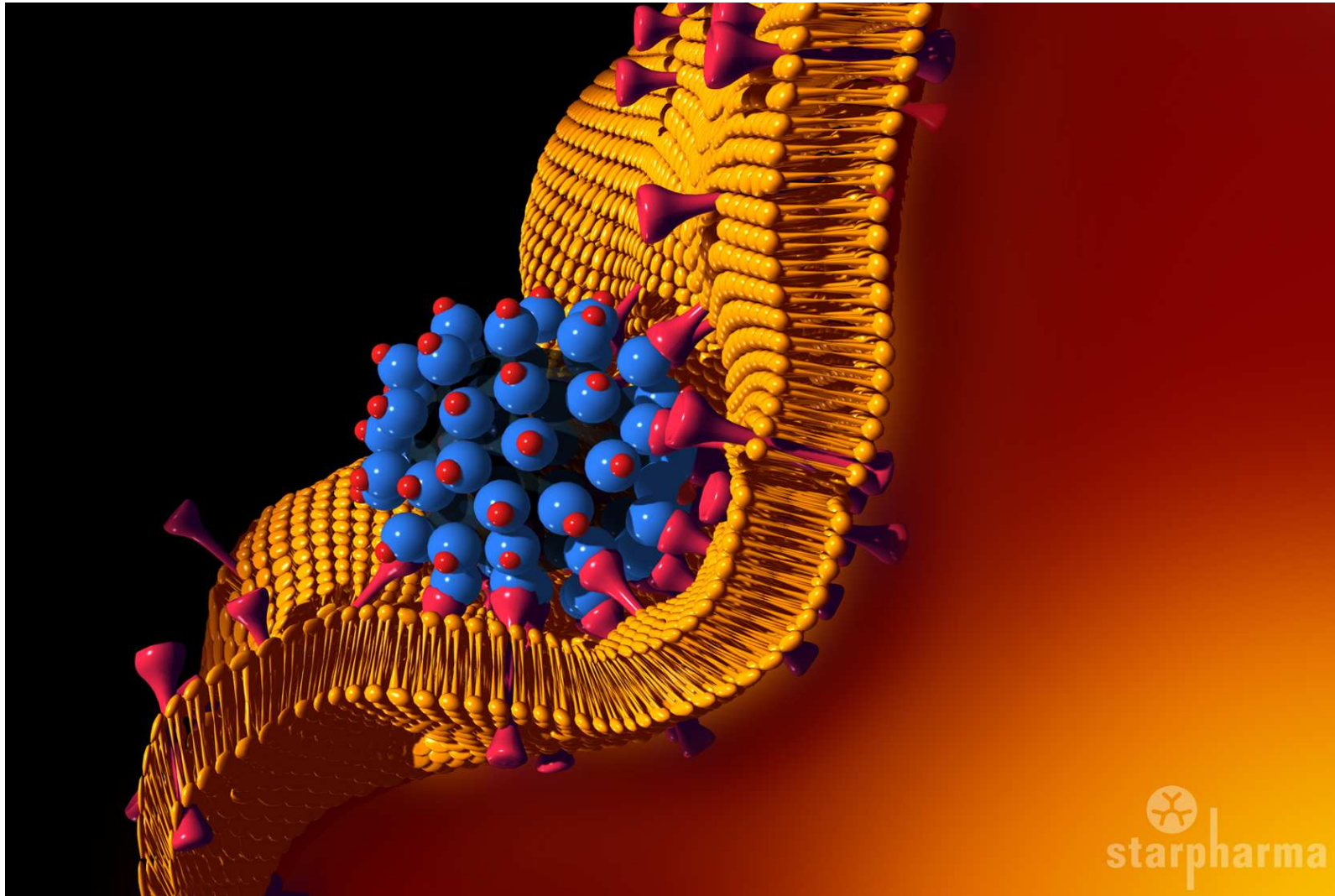
**Modifying Groups
(bio-distribution)**

Traditional Monovalent Drugs



Most small molecule drugs are only capable of monovalent binding.

Dendrimer Based Polyvalent Drugs



Dendrimers are capable of polyvalent (multiple receptor-site) binding to cell or viral receptors.

DNT's Opportunities

Nano - catalysts

Nano - reagents

Nano - optics

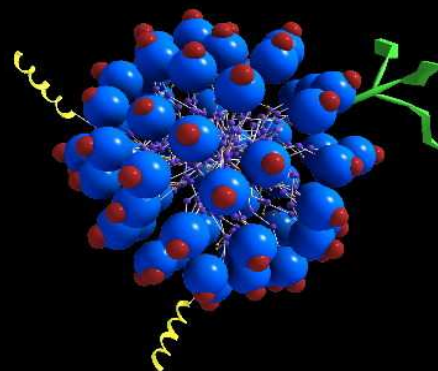
Nano - electronics

Military

Nano - sensors

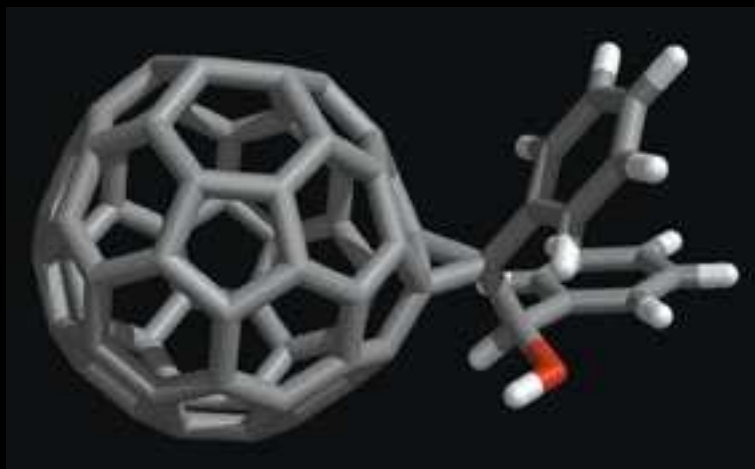
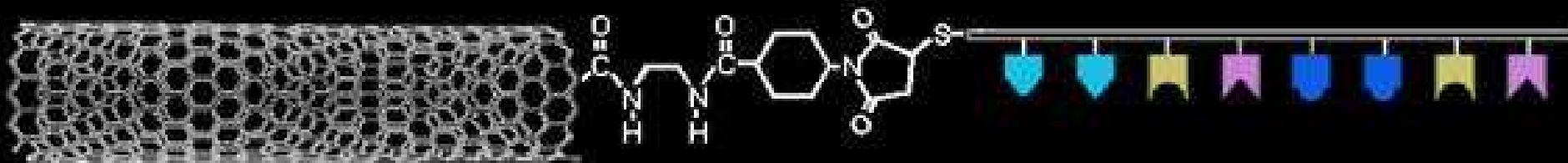
Thin Films

Pharmaceutical



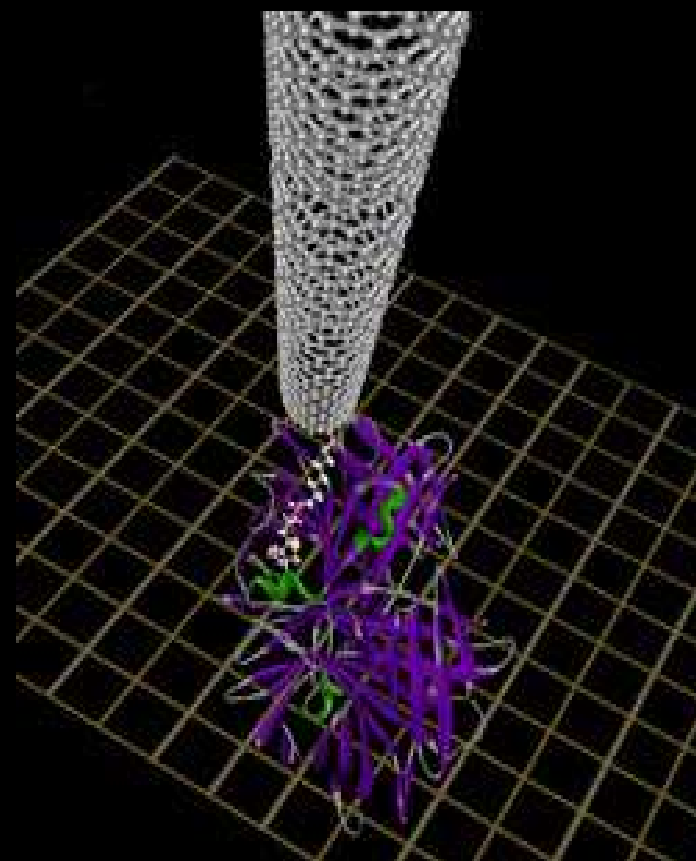
Value Proposition is in Synergistic Opportunity

Carbon Fullerenes – from probes to delivery platforms



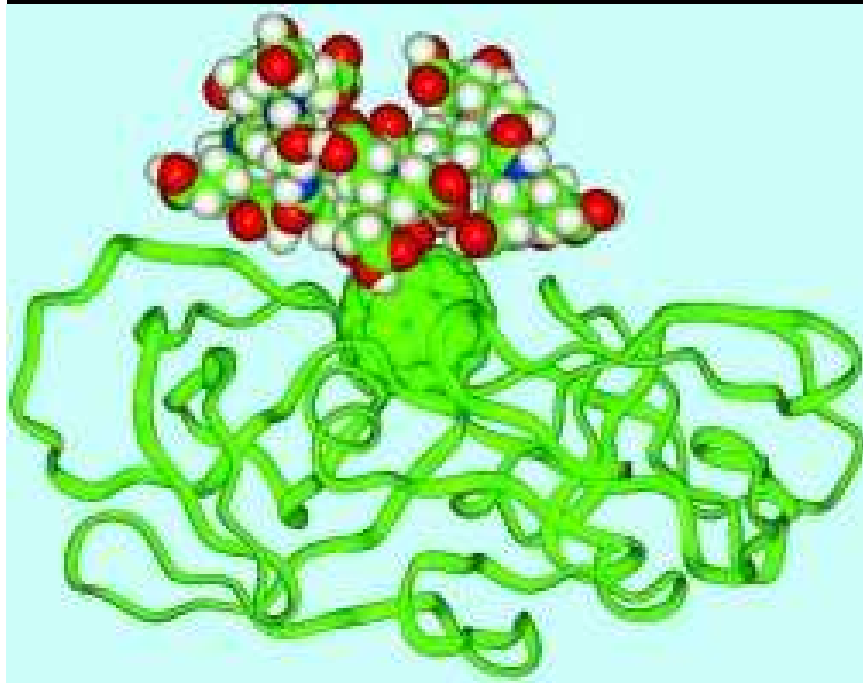
BUCKY DRUG. Model of a fullerene-based HIV protease inhibitor recently designed by Simon Friedman.

3/26/2010



Value Proposition is in Synergistic Opportunity

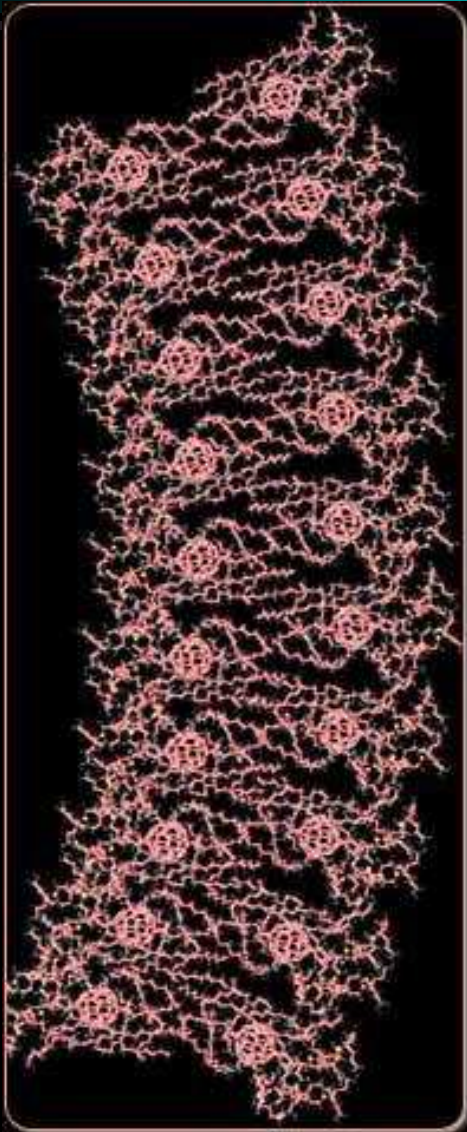
Carbon Fullerenes – from probes to delivery platforms



Fullerene-based protease inhibitor fights HIV by binding to the active site of the protease enzyme (green ribbon). The carbon-60 molecule (green ball) is decorated with various chemical appendages (green, red, white, and blue). C Sixty plans to test it in patients. A. Kirschner/NYU

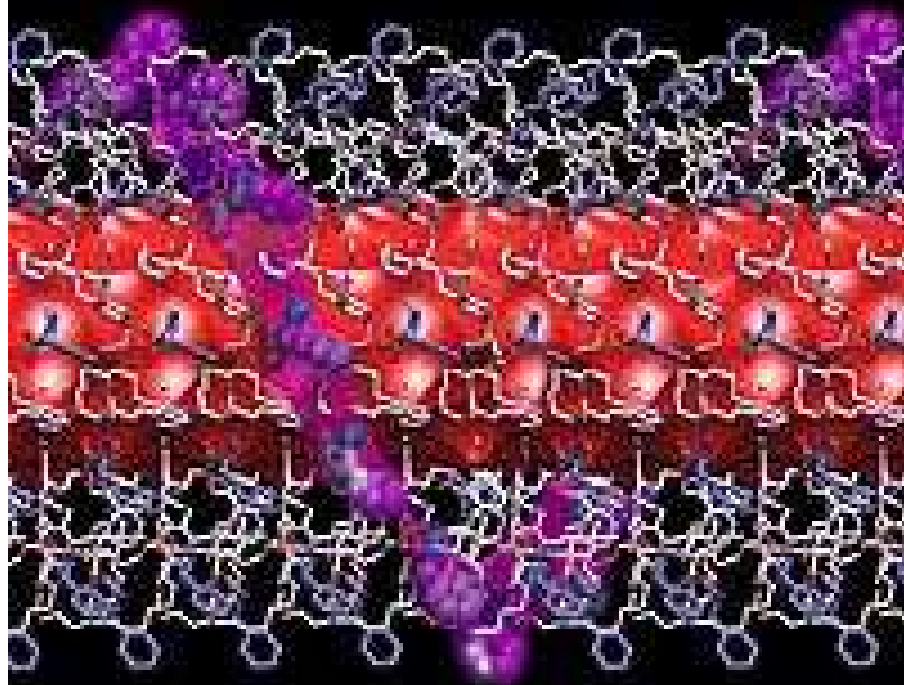
Value Proposition is in Synergistic Opportunity

Carbon Fullerenes – synthetic architectures



*Computer model image of a
fullerene-based artificial membrane
courtesy of Andreas Hirsch, Ph.D.,
University of Erlangen, Germany*

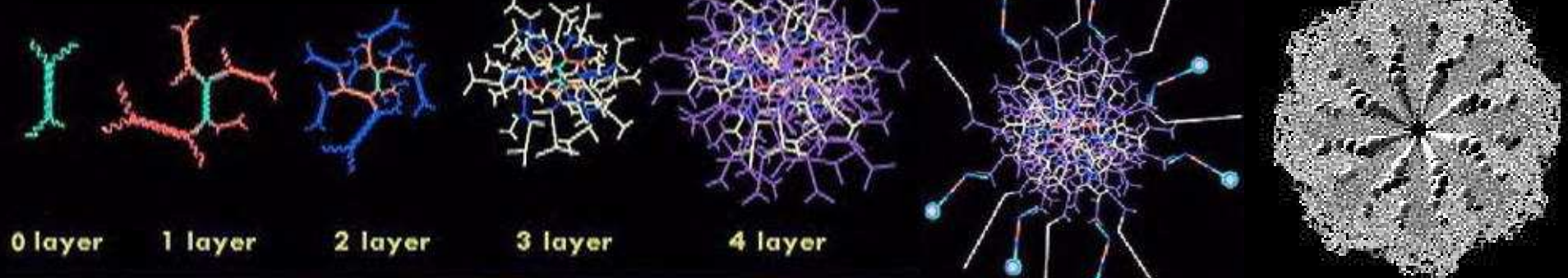
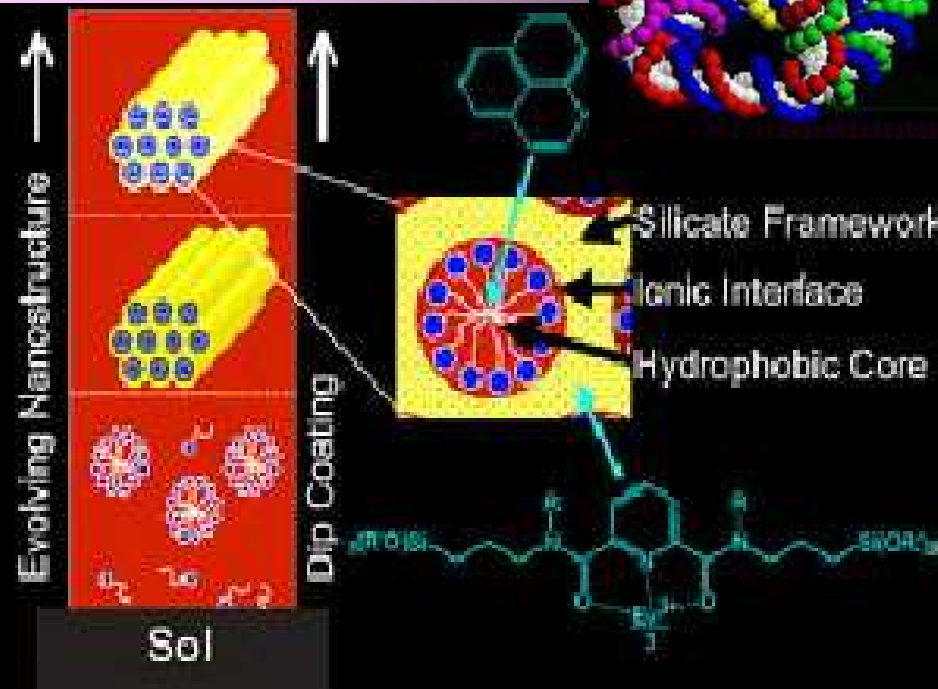
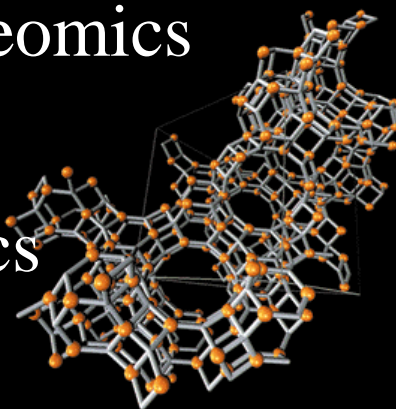
Nanotubes from other materials – polymers, proteins, synthetic organic molecules



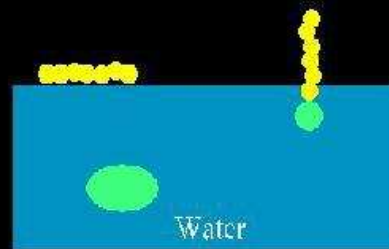
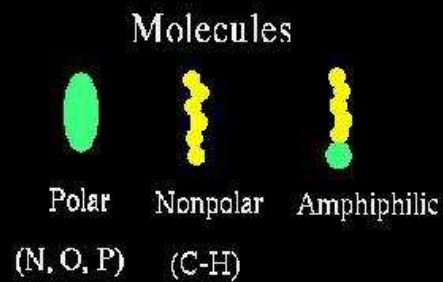
A self-assembled rosette nanotube and its mirror image prepared in the Fenniri laboratory. These materials are now made with predefined chiroptical, physical and chemical properties. The Fenniri group's nanotubes promote their own formation and offer numerous potential applications. (Purdue University Department of Chemistry)

Molecules as Tools – Not Just Endproducts

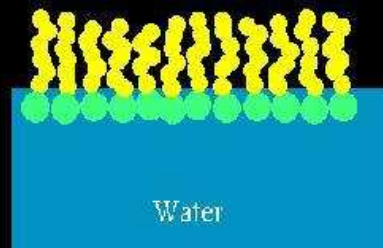
- Nanotubes - carbon, polymer, protein, etc.
- Structural proteomics
- Dendrimers
- Organometallics
- Zeolites



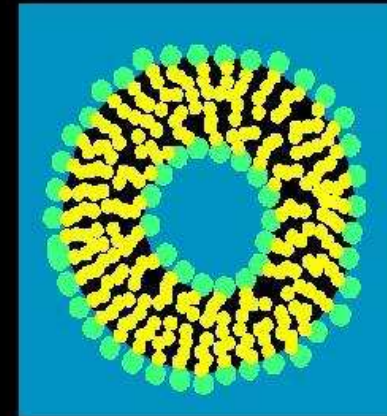
Molecules as Tools - Not Just Endproducts > Complex Nanostructures > Nanodevices



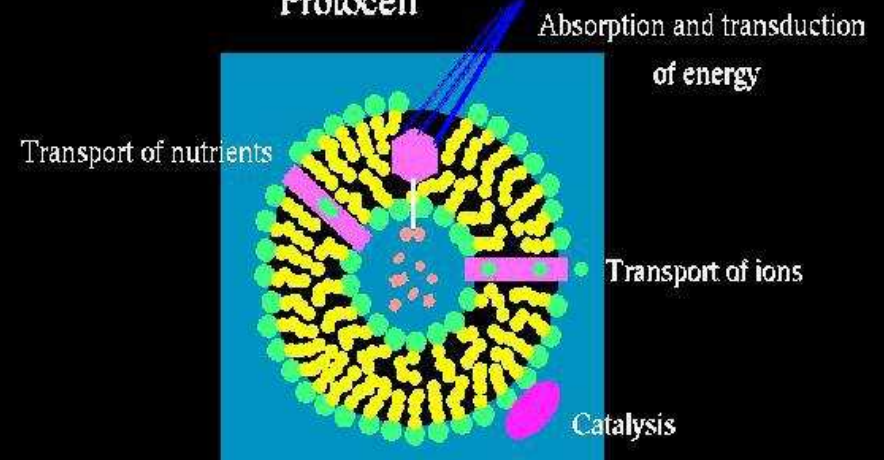
Monolayer of amphiphiles



Bilayer Vesicle



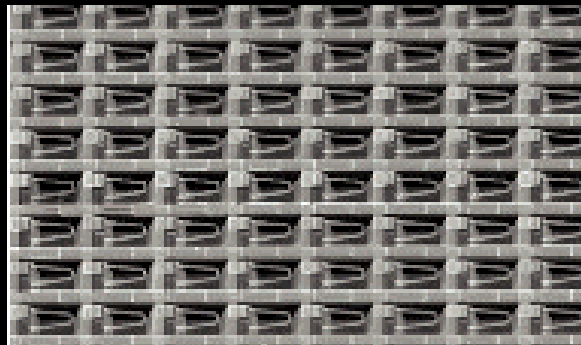
Protocell



Define "Tools"

Goal of the tool is to manipulate molecules and pattern matter

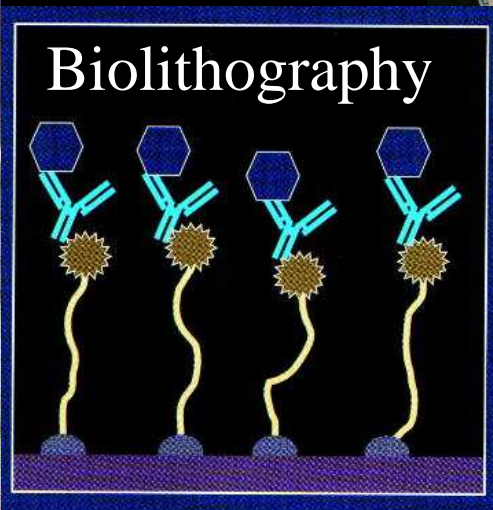
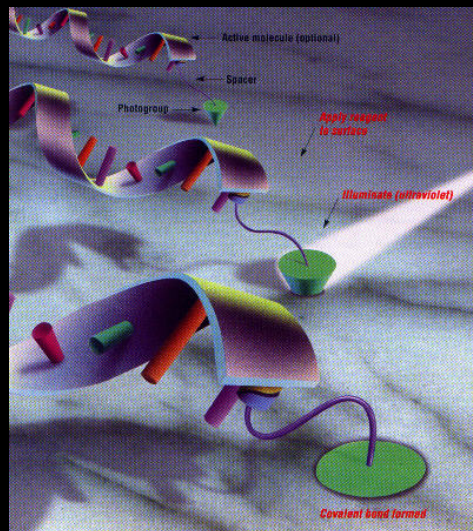
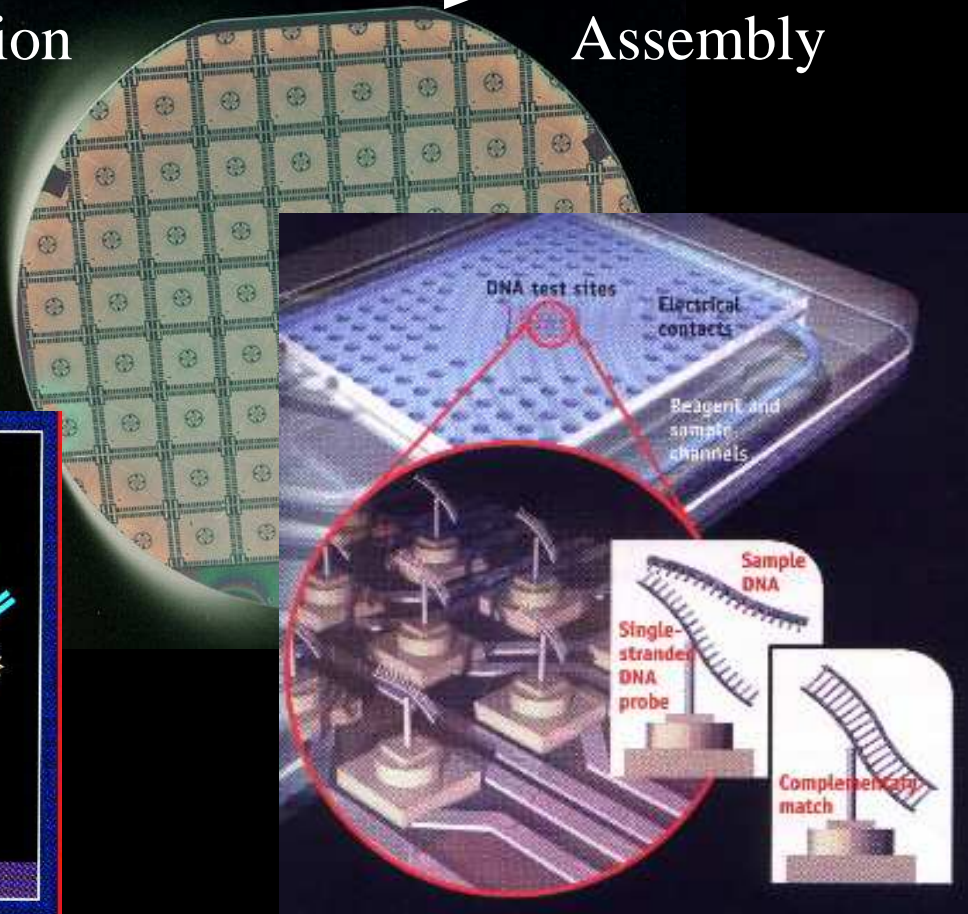
AFM devices / arrays



Electro-Molecular Manipulation

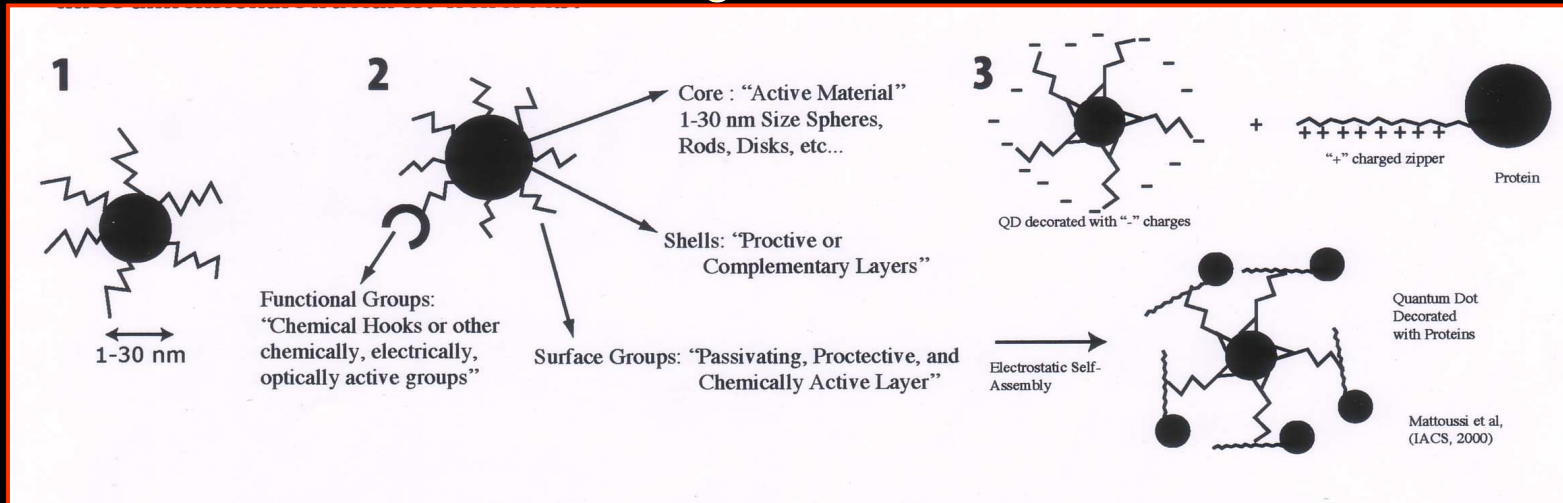


Heterogeneous Assembly

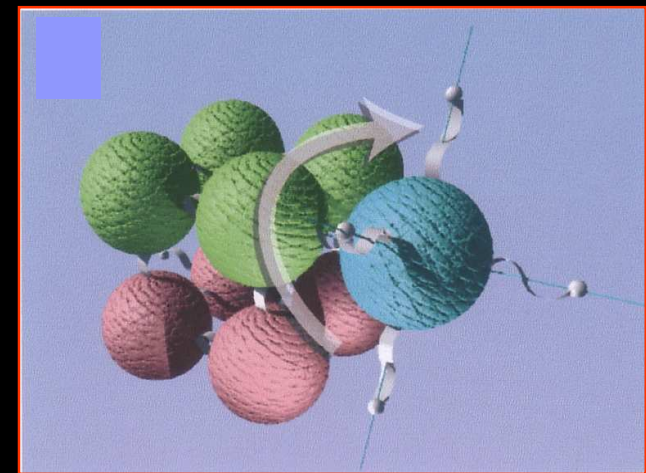
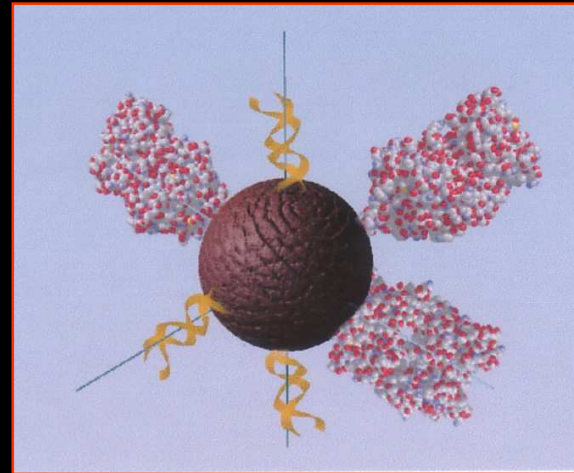
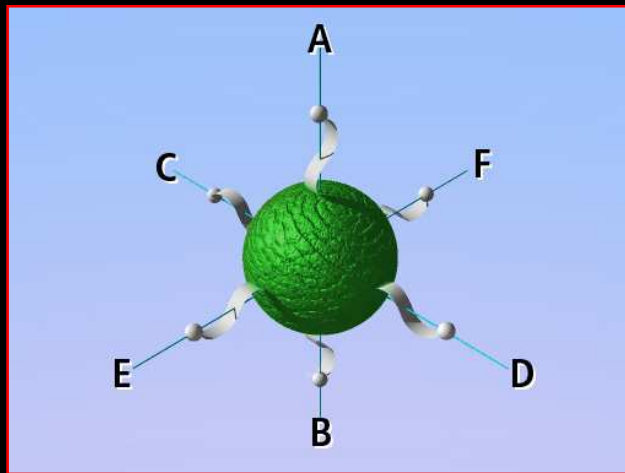


Objective: Improved Processes for Manufacturing High Precision Functionalized Nanostructures

Present strategies for nanofabrication

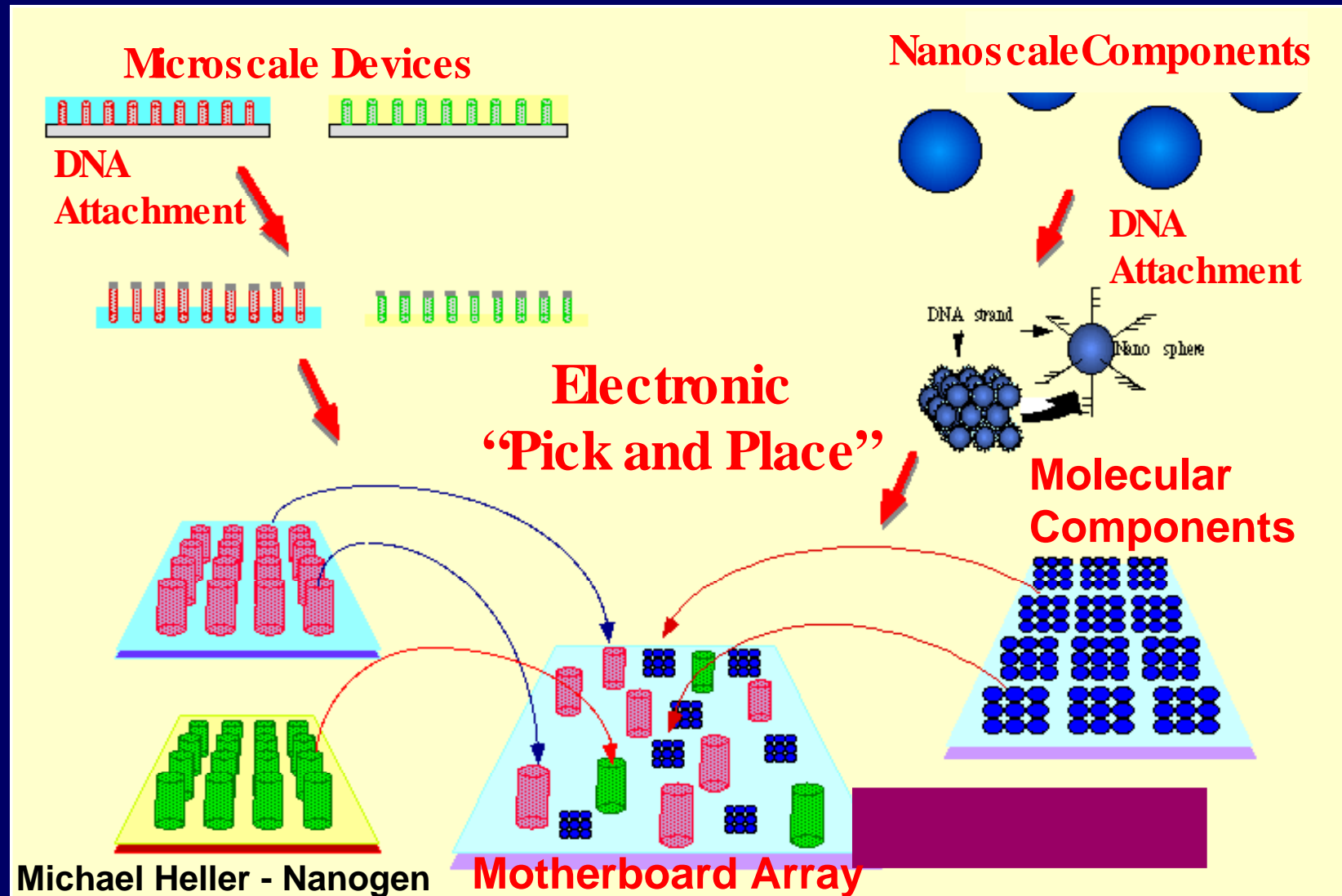


Target future nanofabrication goals



20 nanometers

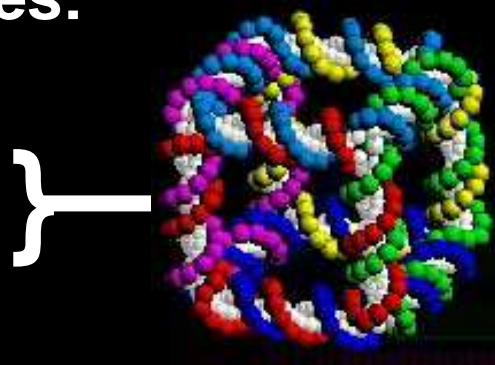
Heterogeneous Integration Process for Micro/Nanofabrication – Synergy of Top-Down with Bottom-Up Processes



Biology as a mechanism for material production, patterning, and fabrication

Key Properties:

**Photonic
Electronic
Mechanical
Chemical**



**Living
Systems as
Biofoundry**



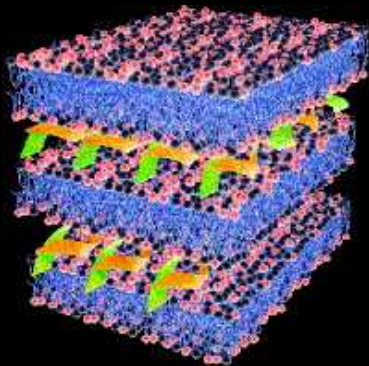
Genetic Magnification

Dynamic Agent

Controlled Replication

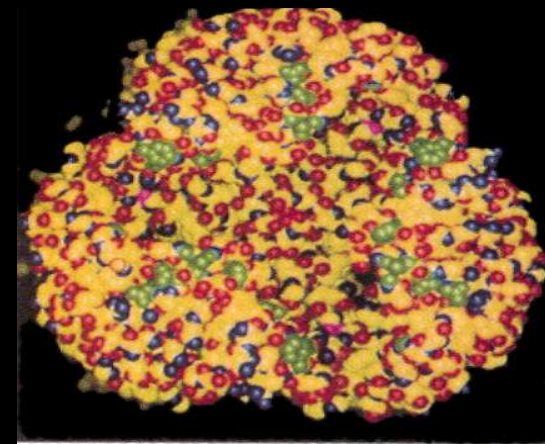
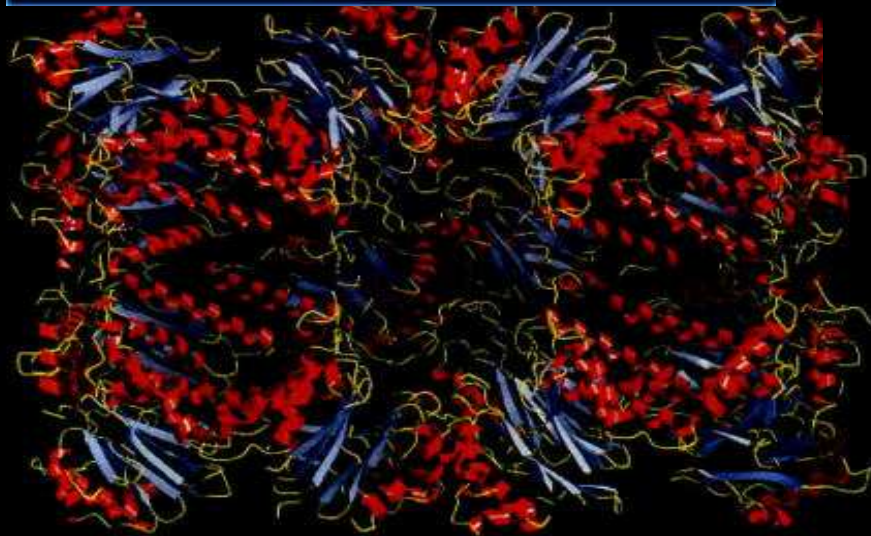
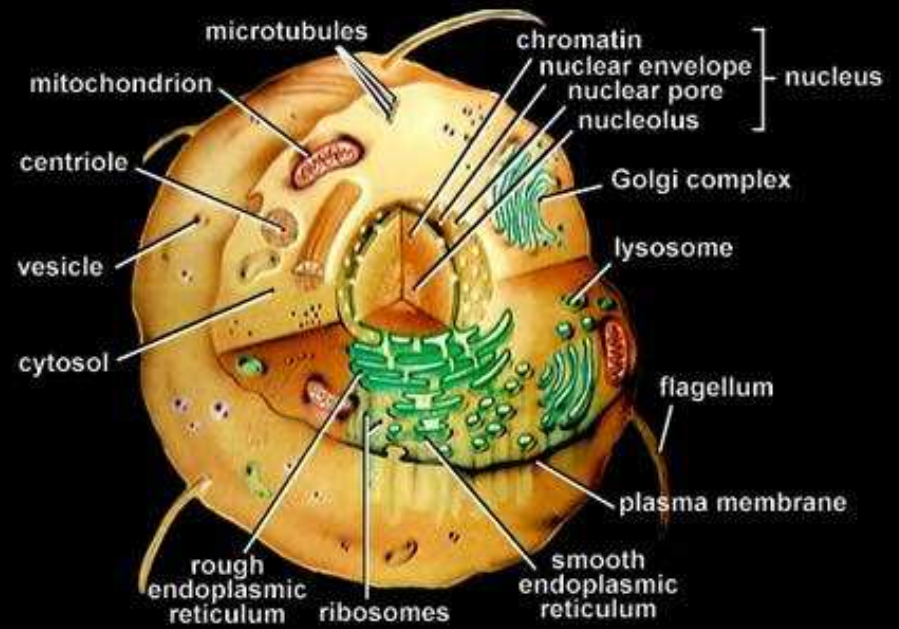
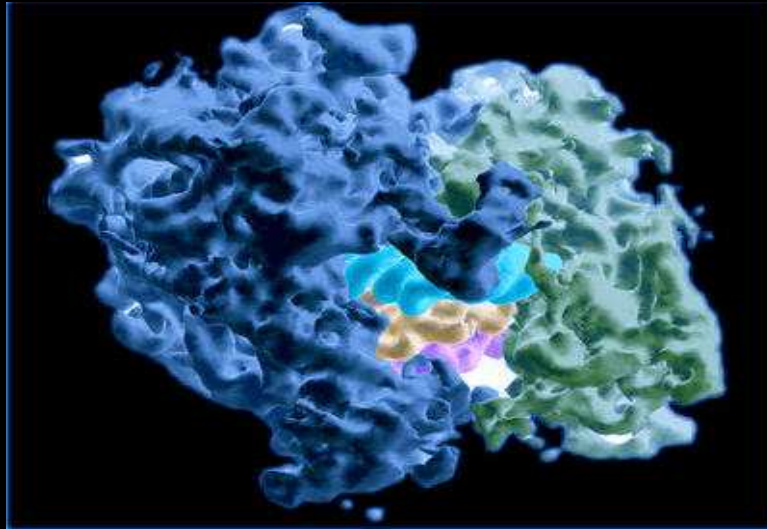
**Material Patterning /
Structural Systems**

**Materials Harvest /
“Biocomponents”**

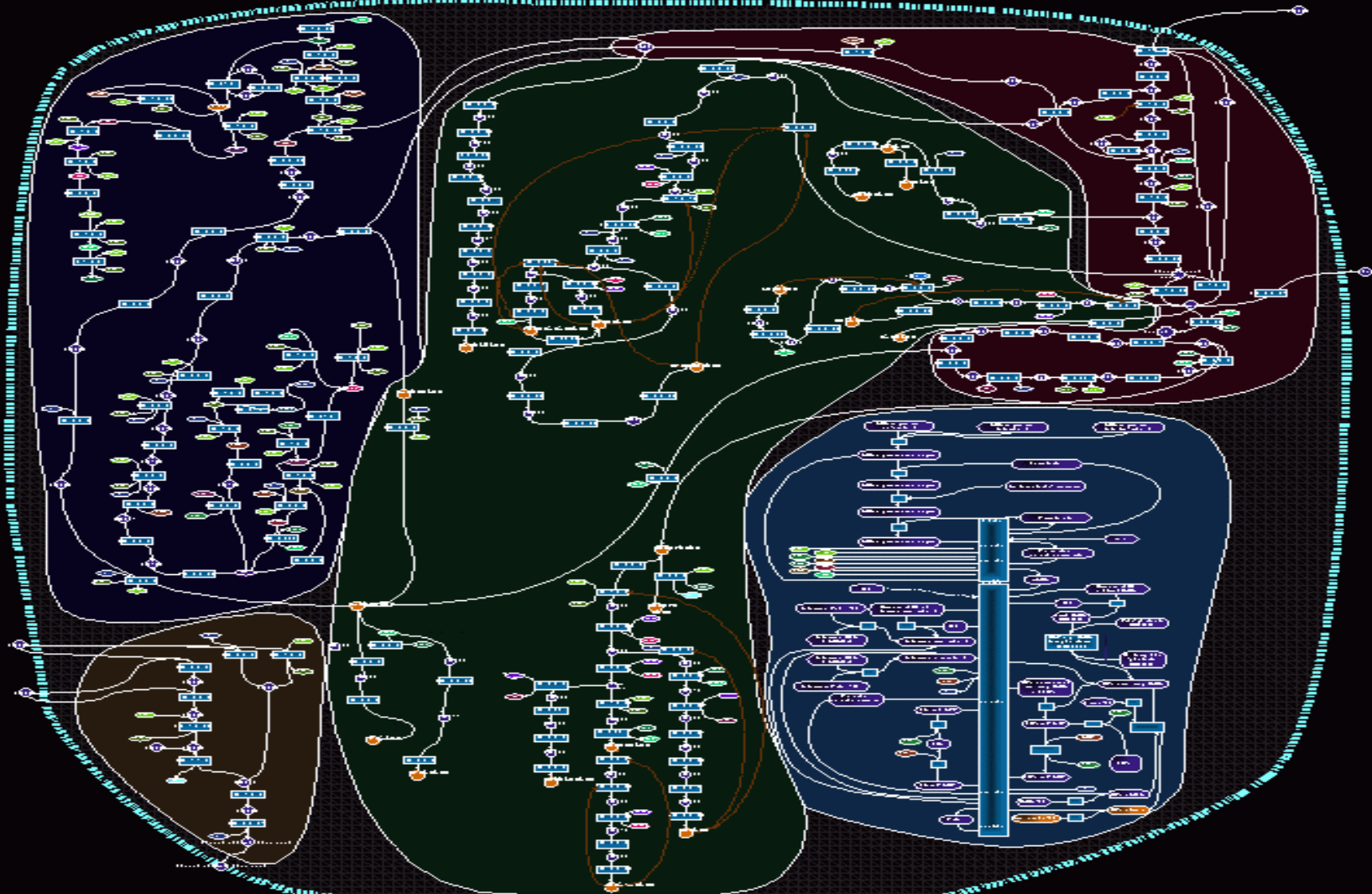


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Nature's Nanofoundries



In-Silico Biology – Schematic Engine of Biological Systems



HOW A GENETIC PART WORKS

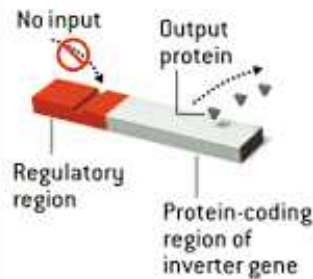
Assemblies of genes and regulatory DNA can act as the biochemical equivalent of electronic components, performing Boolean logic.

A COMPONENT

A biochemical inverter performs the Boolean NOT operation in response to an input signal, in the form of a protein encoded by another gene.

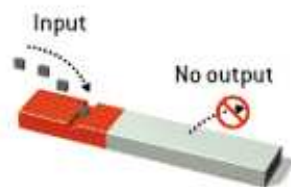
ON

When no input protein is present (input = 0), the inverter gene is "on"—it gives rise to its encoded protein (output = 1).



OFF

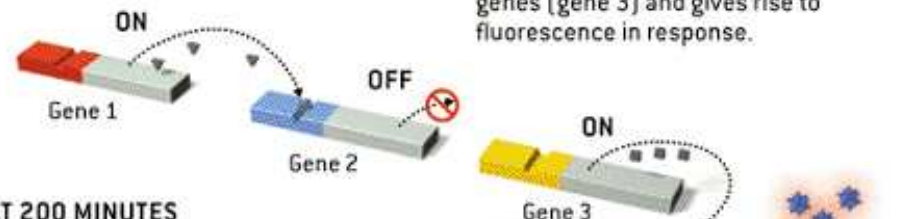
When input protein is abundant (input = 1), the inverter gene turns off (output = 0).



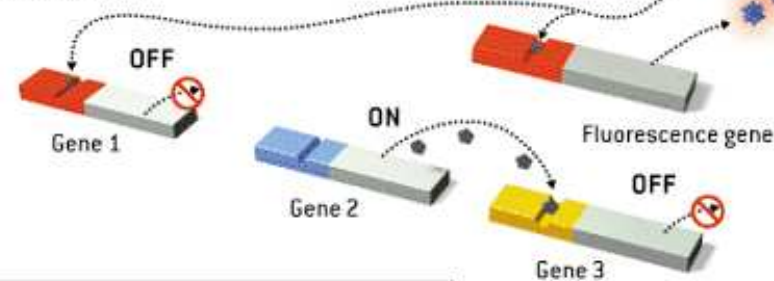
A CIRCUIT

One simple genetic circuit connects three inverters, each of which contains a different gene (gene 1, 2 or 3). The genes oscillate between on and off states as the signal propagates through the circuit. The behavior is monitored through a gene (*far right*) that intercepts some of the output protein generated by one of the inverter genes (gene 3) and gives rise to fluorescence in response.

AT 150 MINUTES

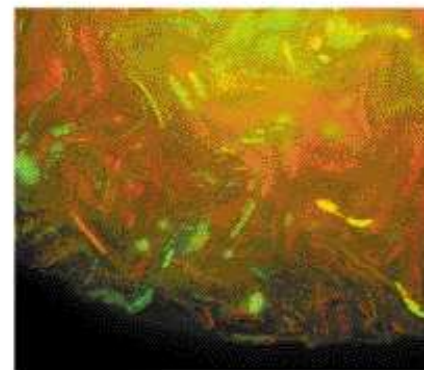
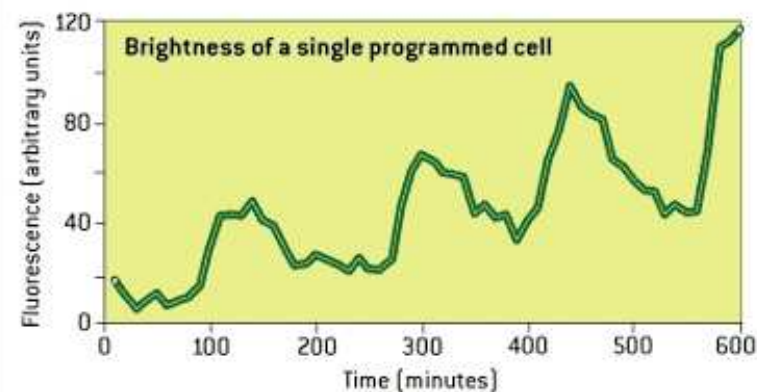


AT 200 MINUTES



A CIRCUIT IN ACTION

Cells containing such a circuit blink on and off repeatedly (*graph*). But in practice, identically altered cells in a culture (*photograph*) blink at varying rates, because genetic circuits are noisier and less controllable than electronic ones.



From Reductionism to Integrated Systems Biology

- understanding the information content encoded in biological networks
- mapping the design rules for progressively greater complexity of biological order



gene(s)



pathways, circuits and networks



progressively ordered assemblies: organelles, cells, tissues, organs



**homeostatic integration of myriad, complex, interactive networks
(physiology)**

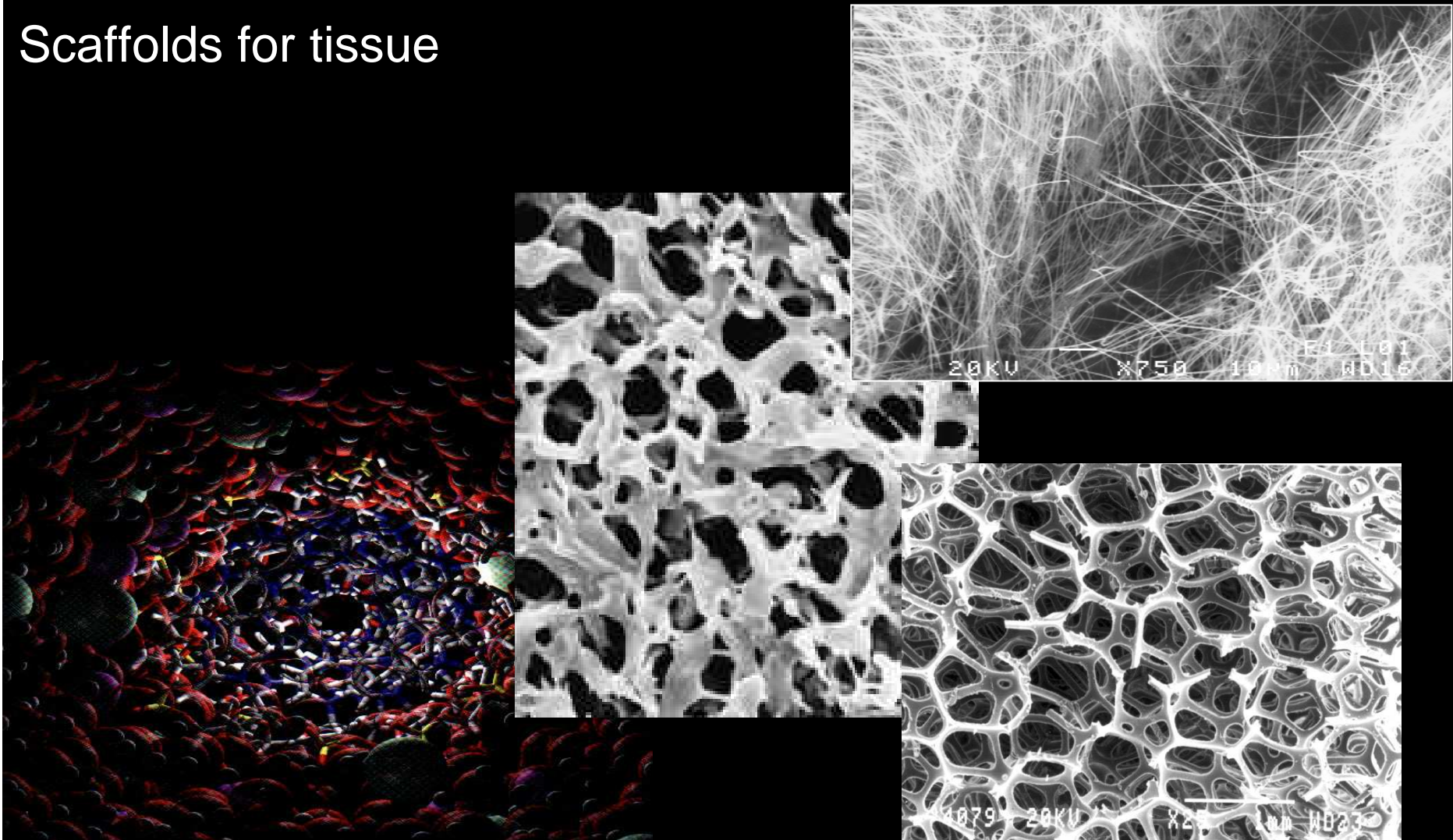
Dr. George Poste
Director

Address: [george.poste](mailto:george.poste@asu.edu)
Server: asu.edu

Enhanced Biology . . .

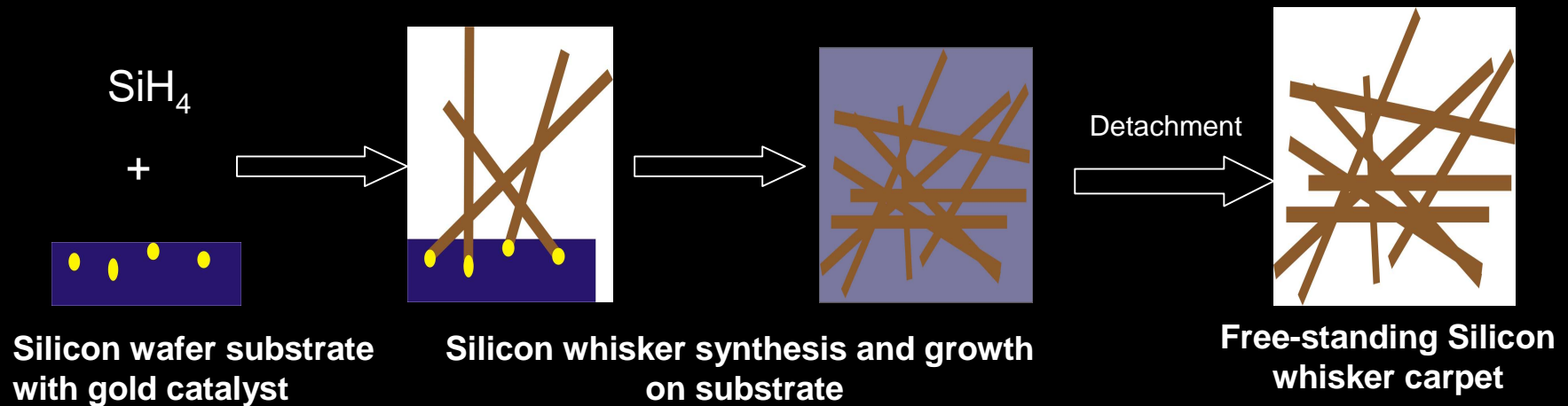
Nanostructured Cellular Environments

Scaffolds for tissue





“top-down” porous silicon fabrication



Non-resorbable “bottom-up” porous mesh based on Si wires

3/26/2010



Jeff Coffer -TCU - j.coffer@tcu.edu

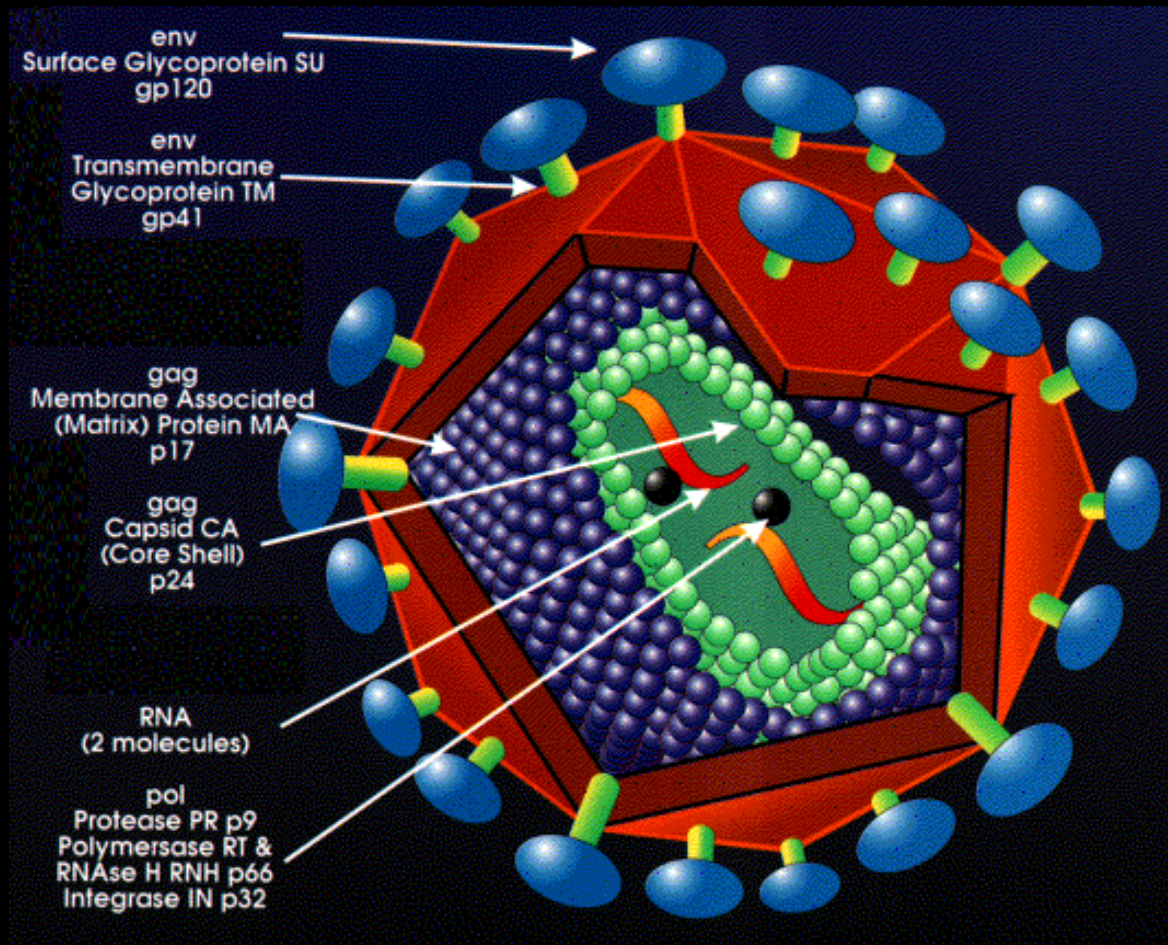
Synthetic Biology . . .

How far will this paradigm go?

Artificial Immune System

Synthetic Antibodies

Bionic Cells



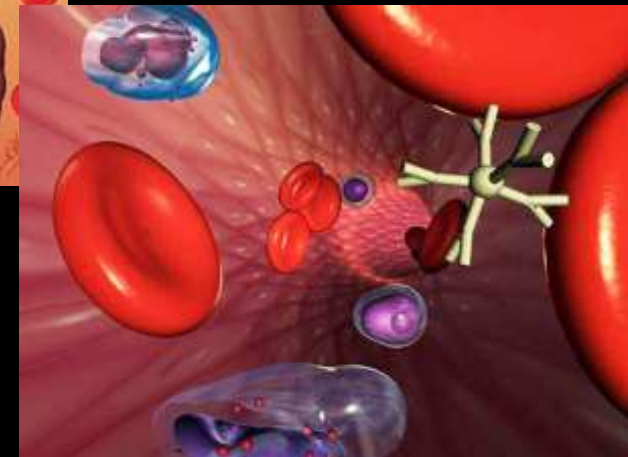
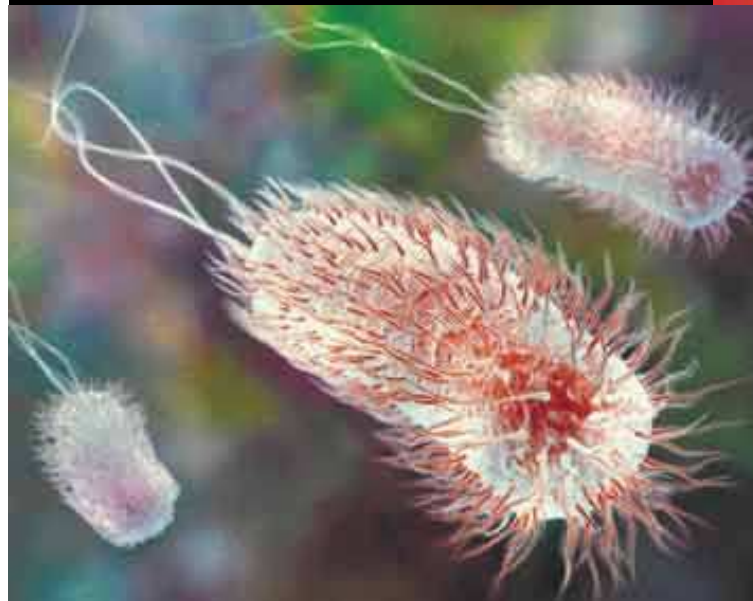
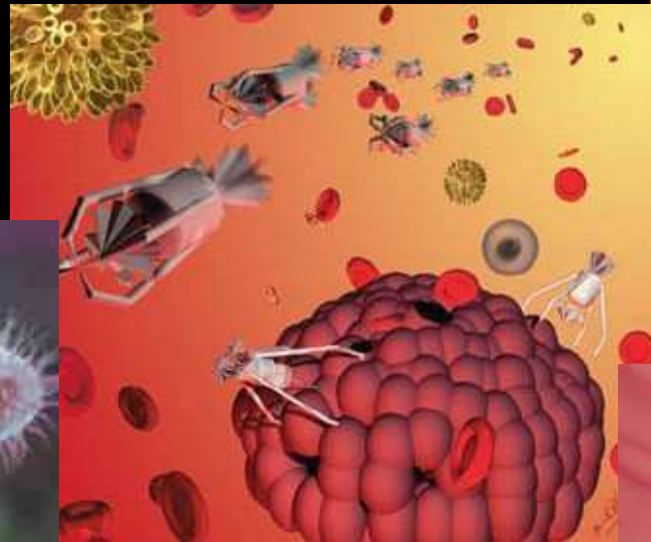
Synthetic Biology . . .

How far will this paradigm go?

Artificial Immune System

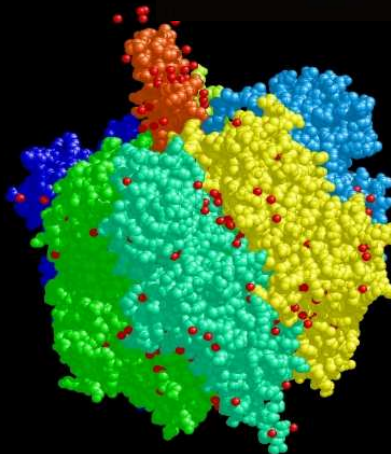
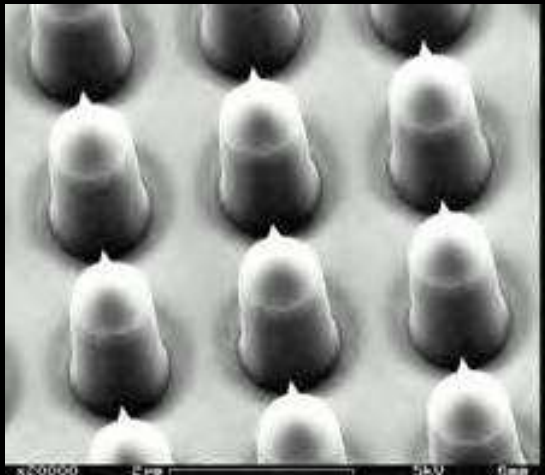
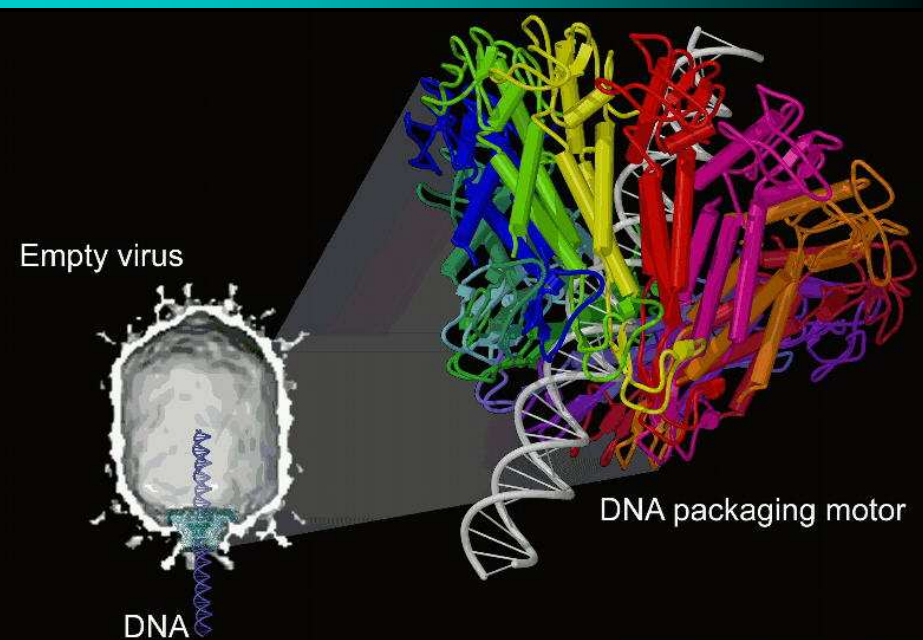
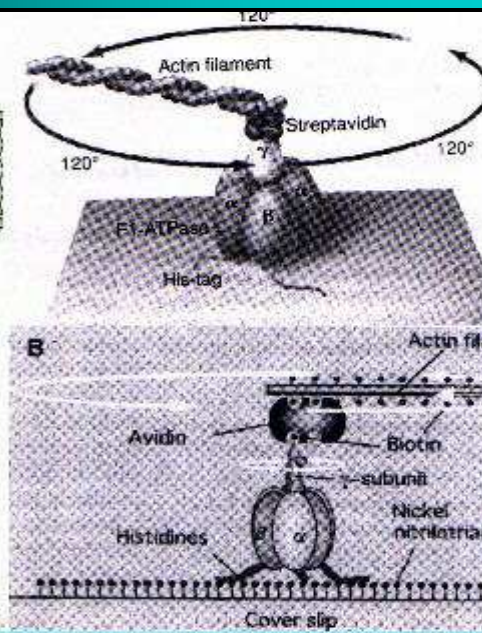
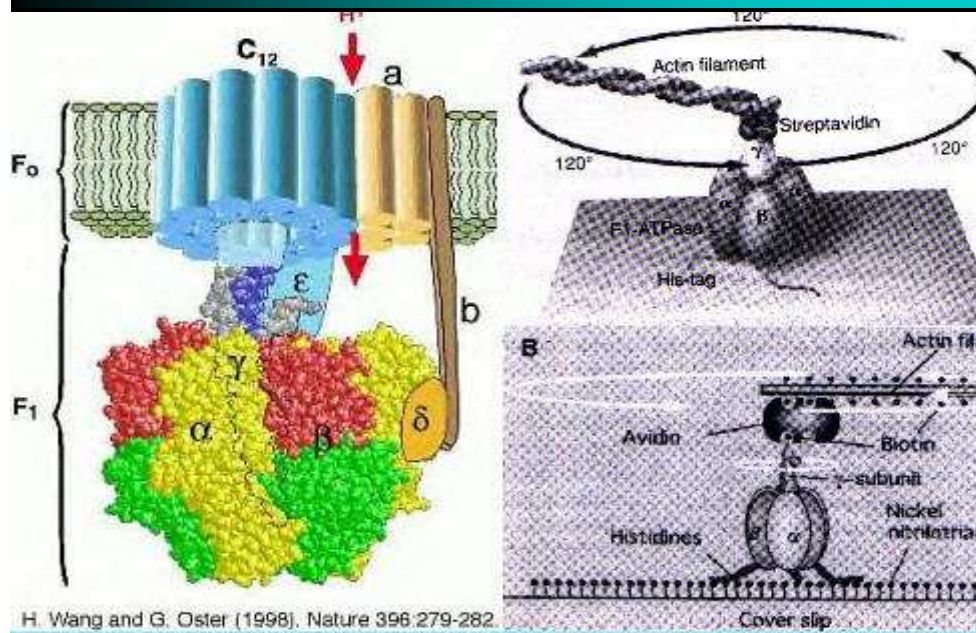
Synthetic Antibodies

Bionic Cells



Synthetic Biology . . .

How far will this paradigm go?



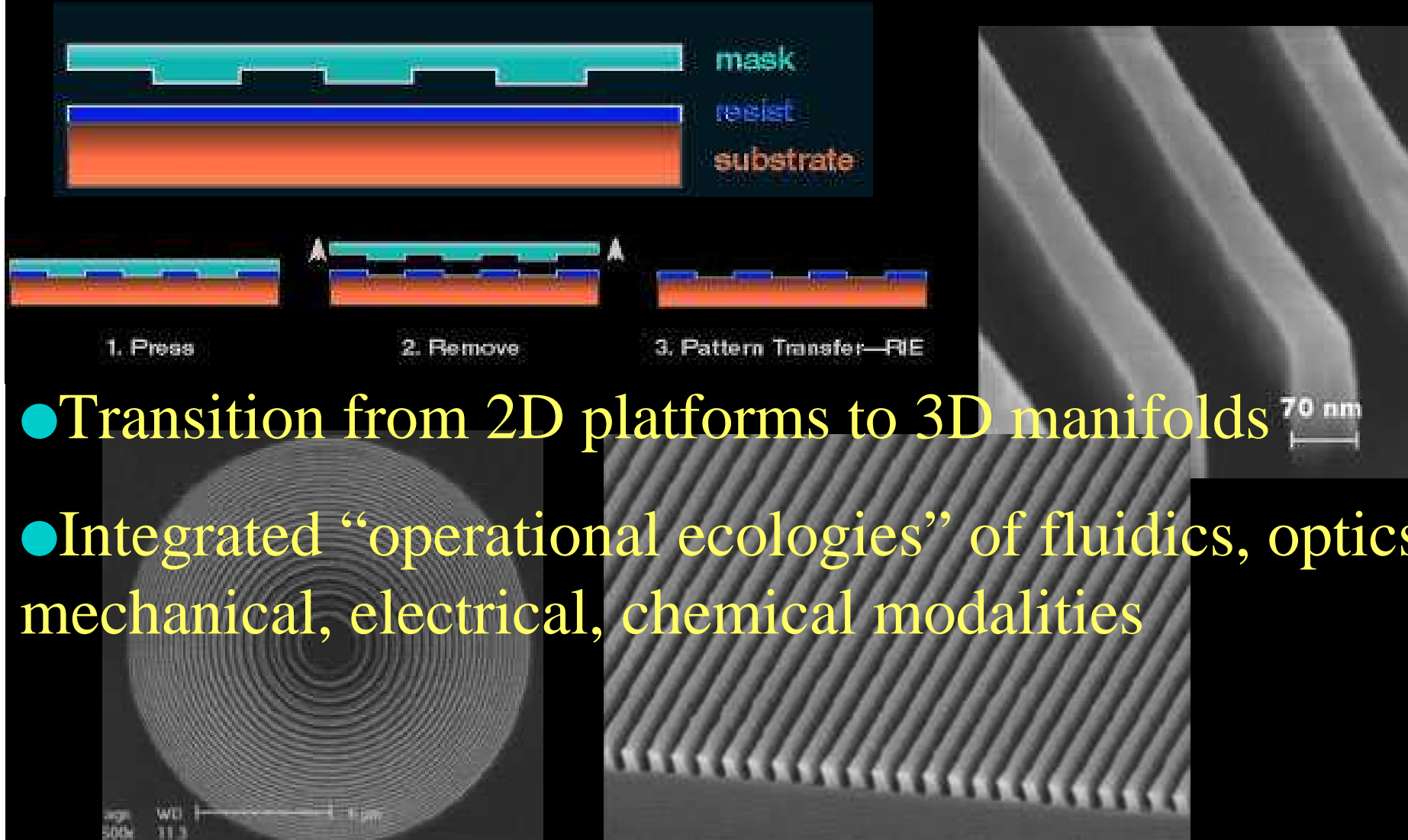
Synthetic Biology . . .

How far will this paradigm go?



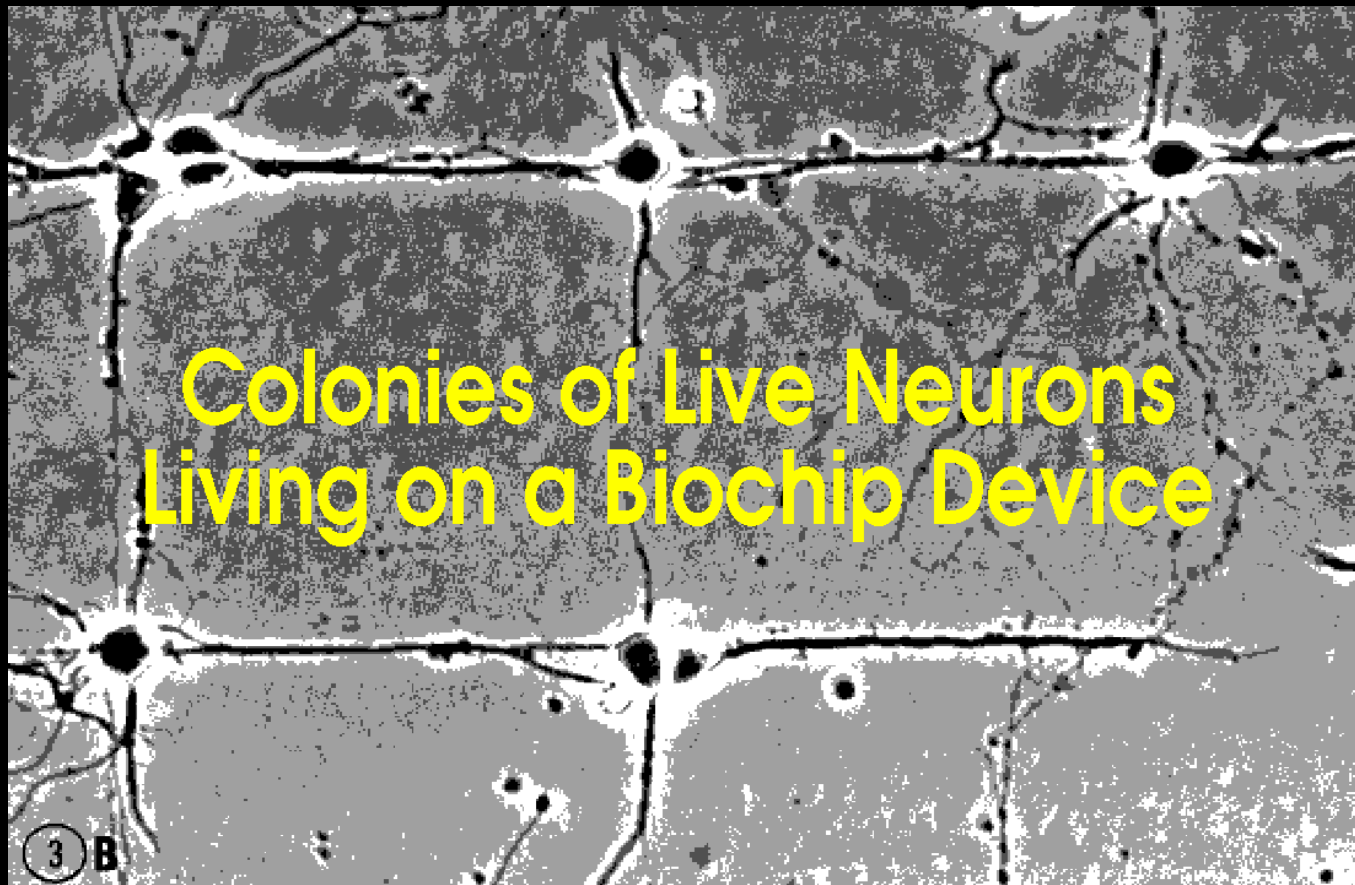
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Synergistically Enabling Foundry Processes in Photonics, Electronics, Fluidics – NanoImprinting



- Transition from 2D platforms to 3D manifolds
- Integrated “operational ecologies” of fluidics, optics, mechanical, electrical, chemical modalities

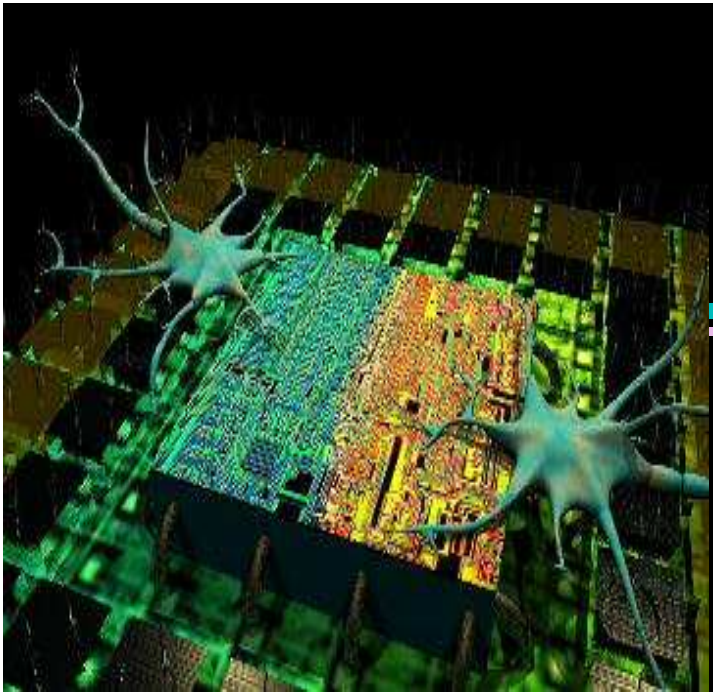
Biopathogen Detection – Live Cells as Sensors



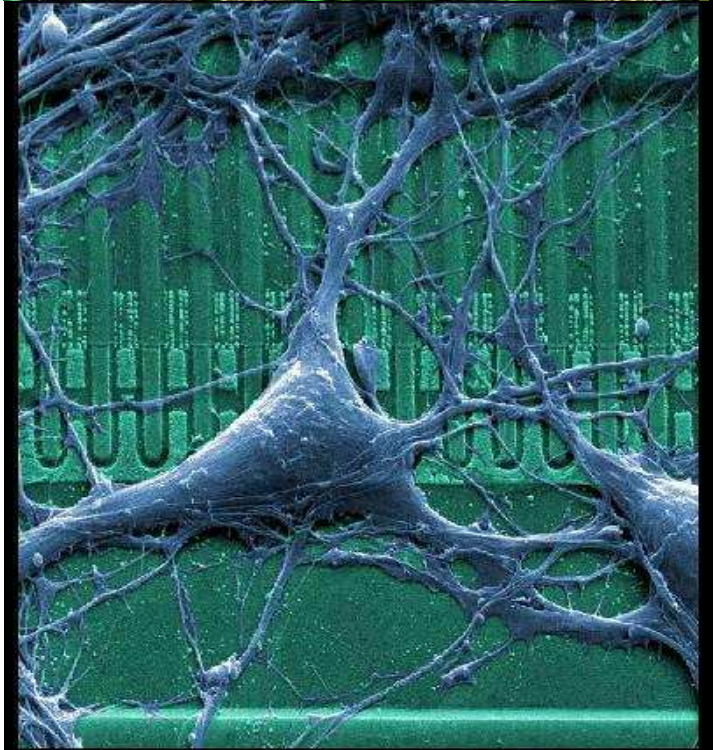
3/26/2010

HIPPOCAMPUS REPLACEMENT

Chip takes over the processing of nervous signals normally performed by the hippocampus

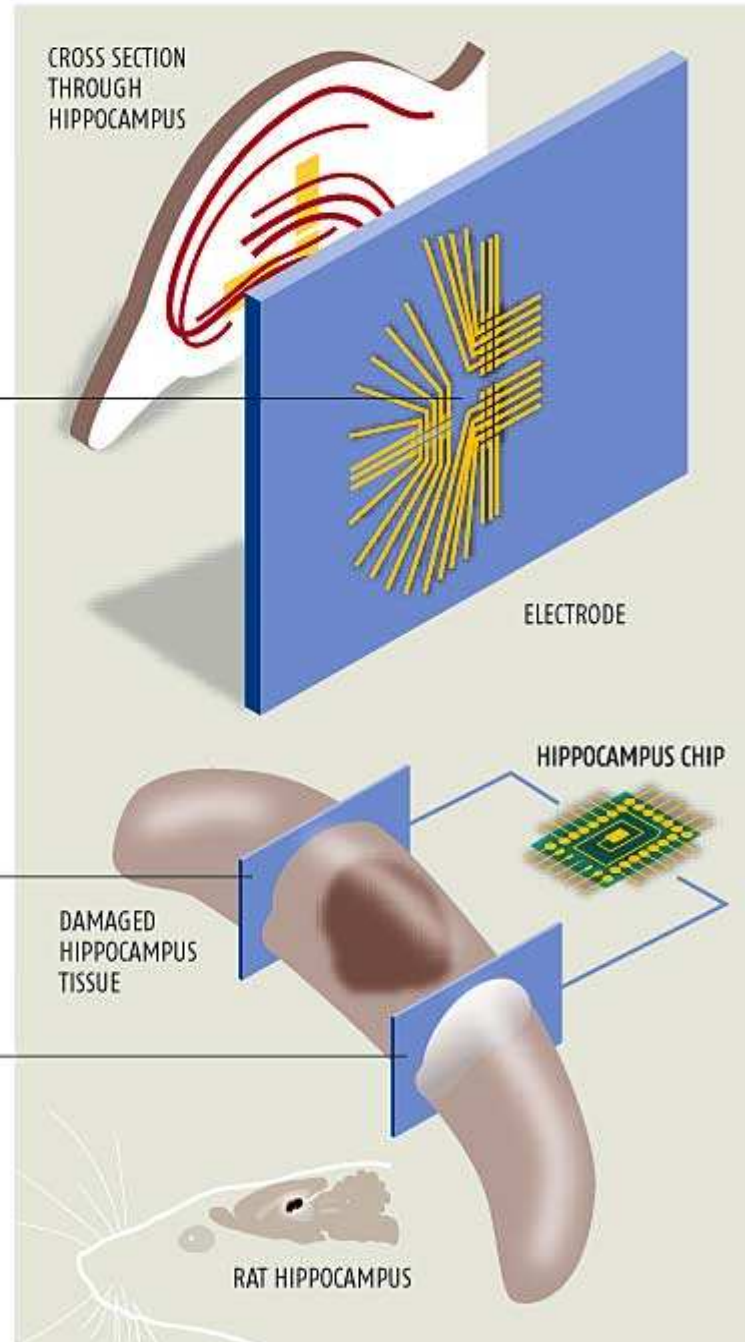


Multiple electrodes are placed on each array. They are positioned to mimic the structure of nerve tissue within a slice of the hippocampus, and make contact with other parts of the brain

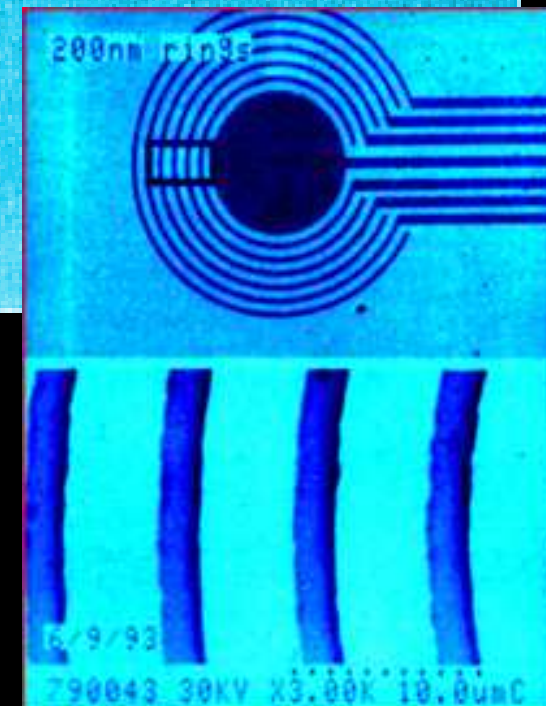
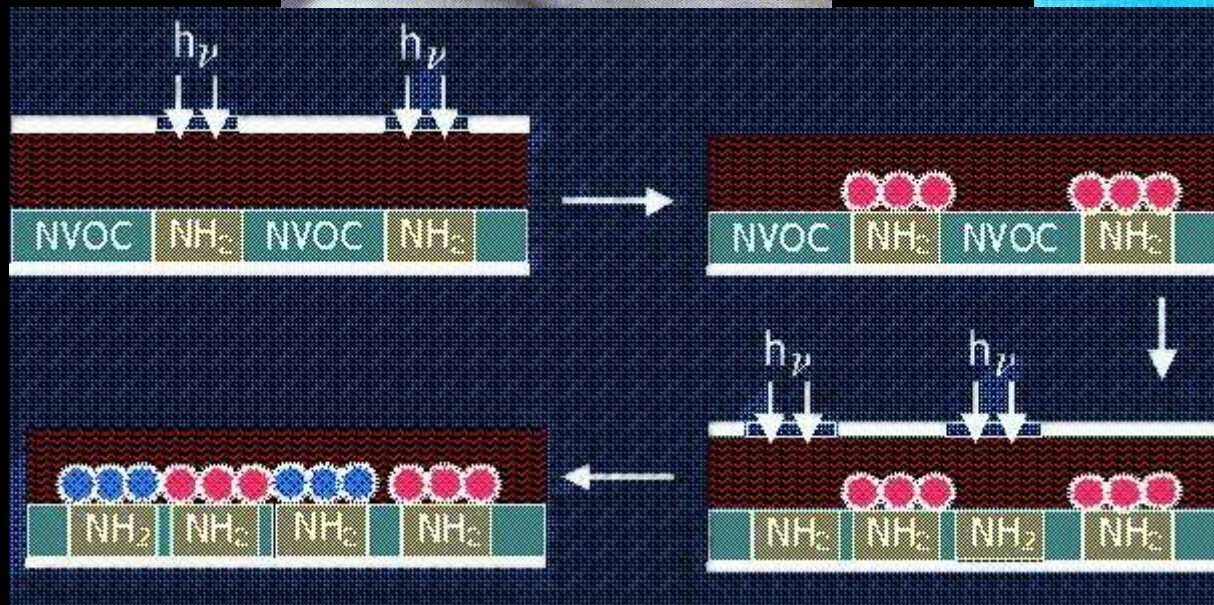
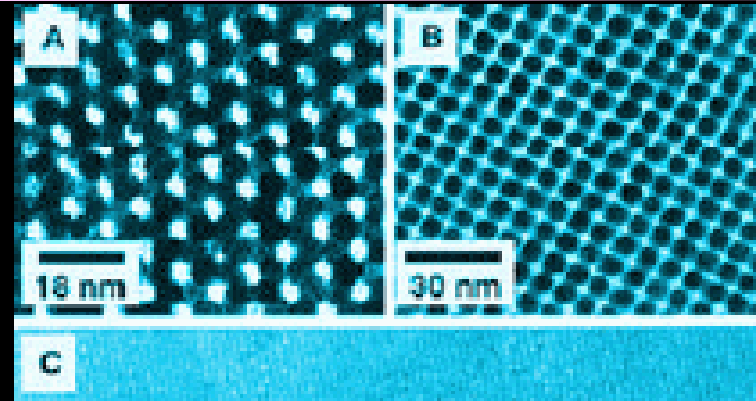
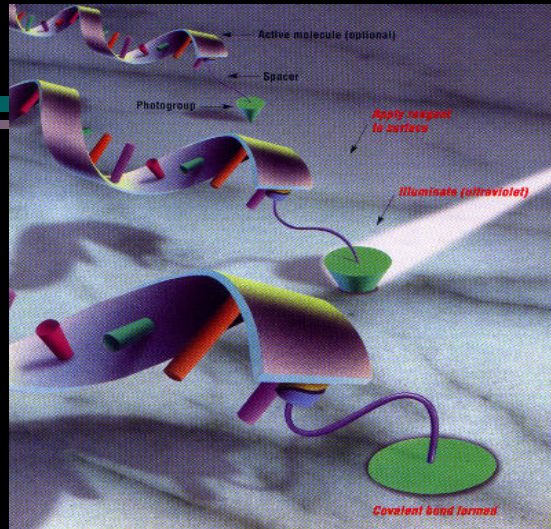


Recording electrode array "listens" to neuron activity coming into the hippocampus and feeds it to the chip

Stimulating electrode array delivers the appropriate electrical output to the rest of the brain



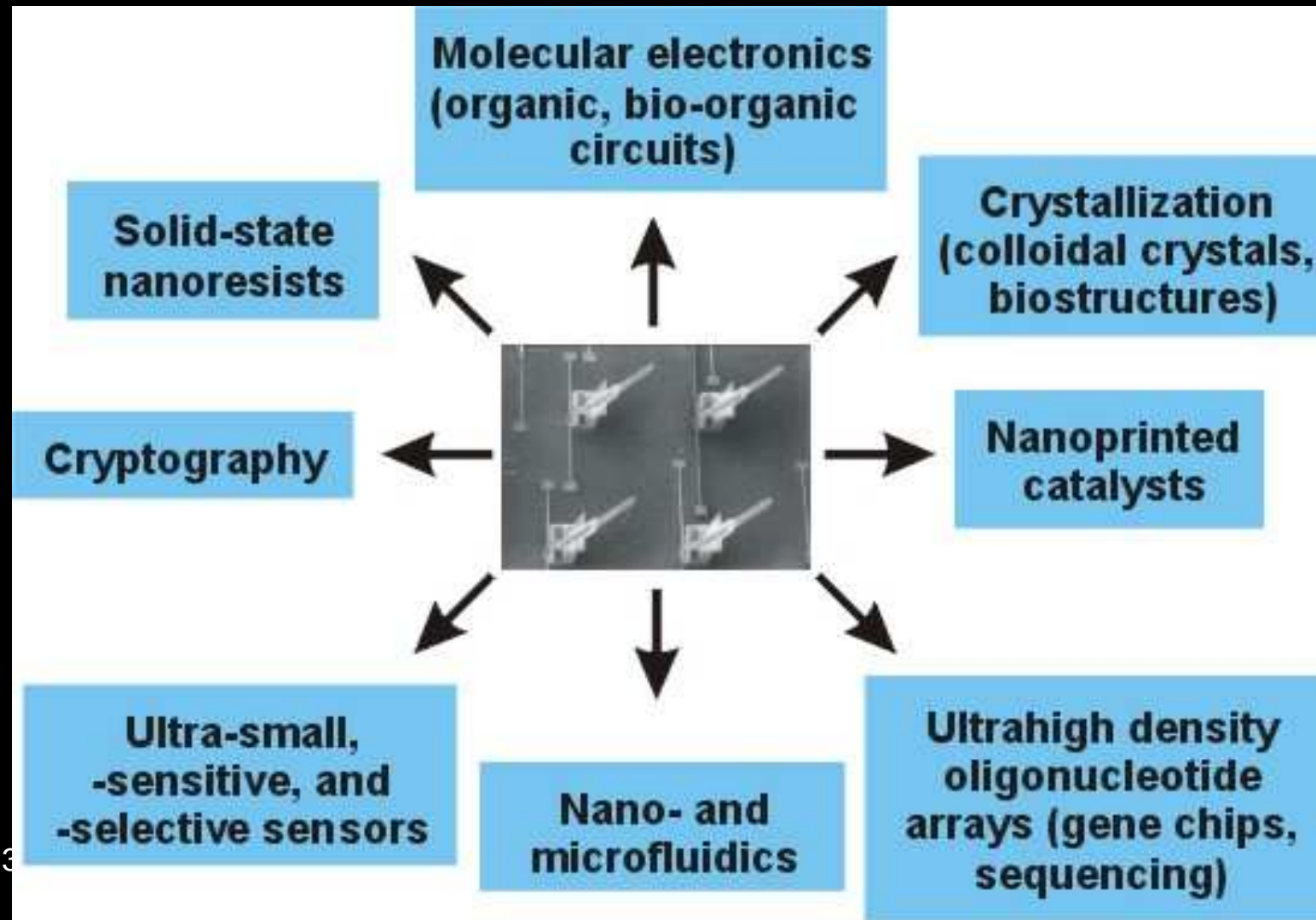
Biolithography – Directed Biochemical Assembly



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Value Proposition is in Synergistic Opportunity

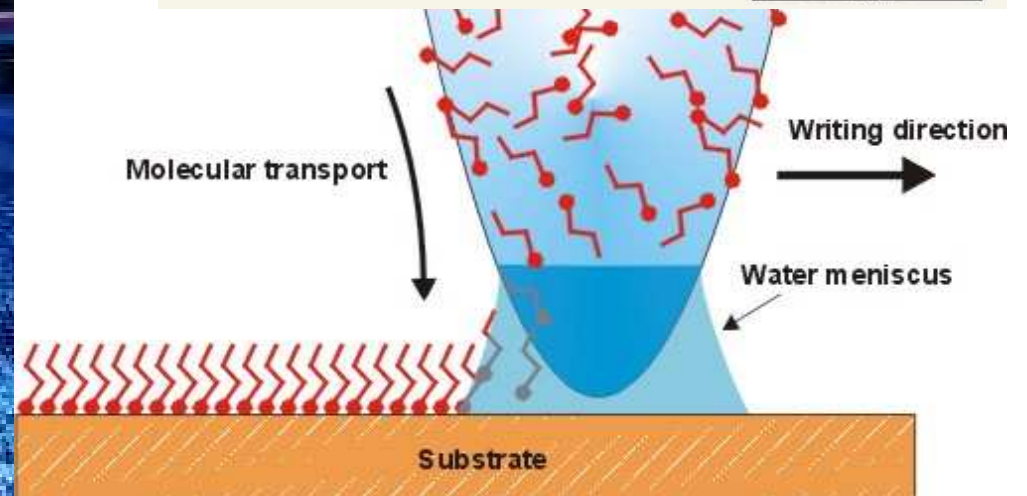
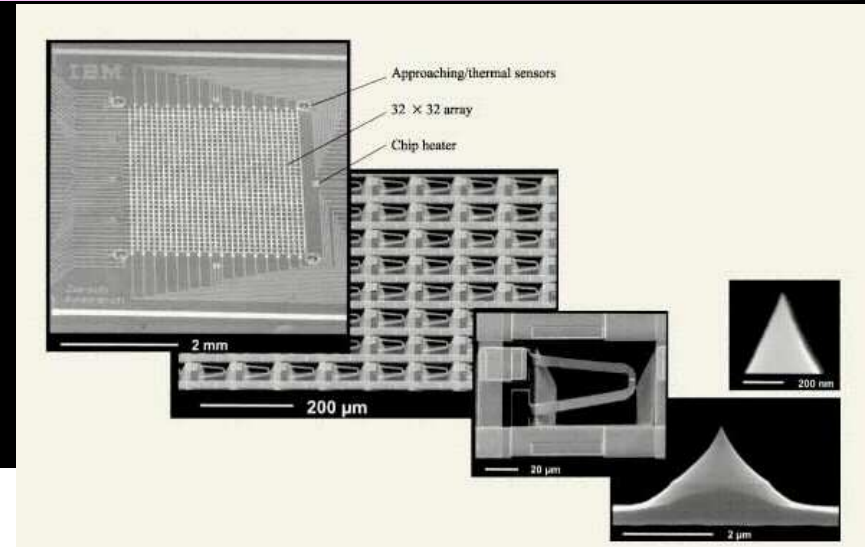
Example - AFM arrays



Value Proposition is in Synergistic Opportunity

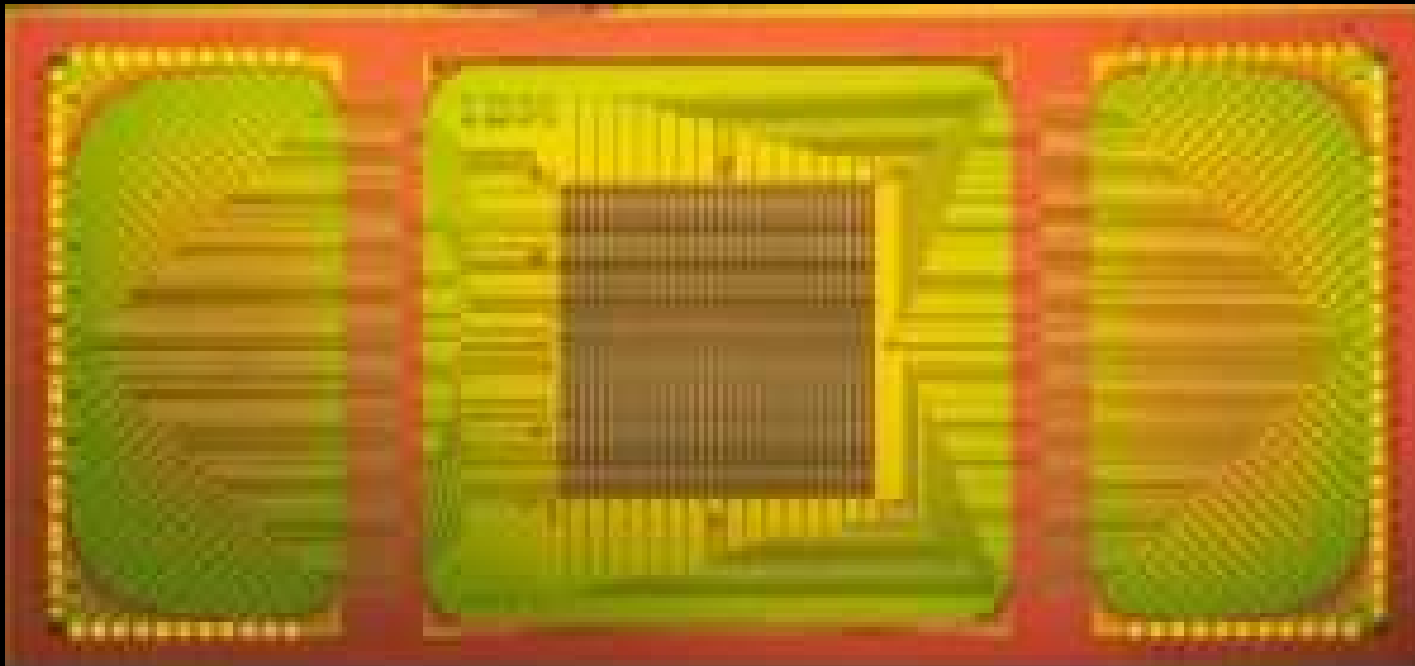
Example - AFM arrays

- Enabling platform for data storage
- Massively parallel molecular deposition



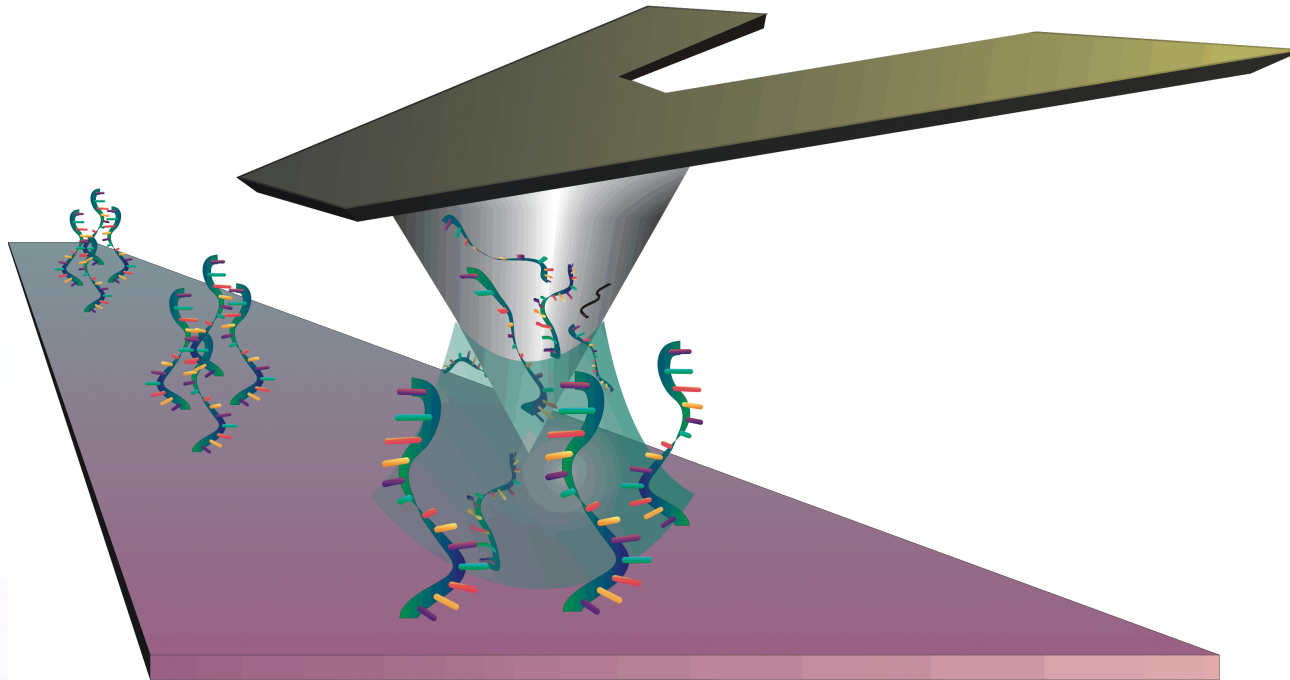
Value Proposition is in Synergistic Opportunity

Example - AFM arrays



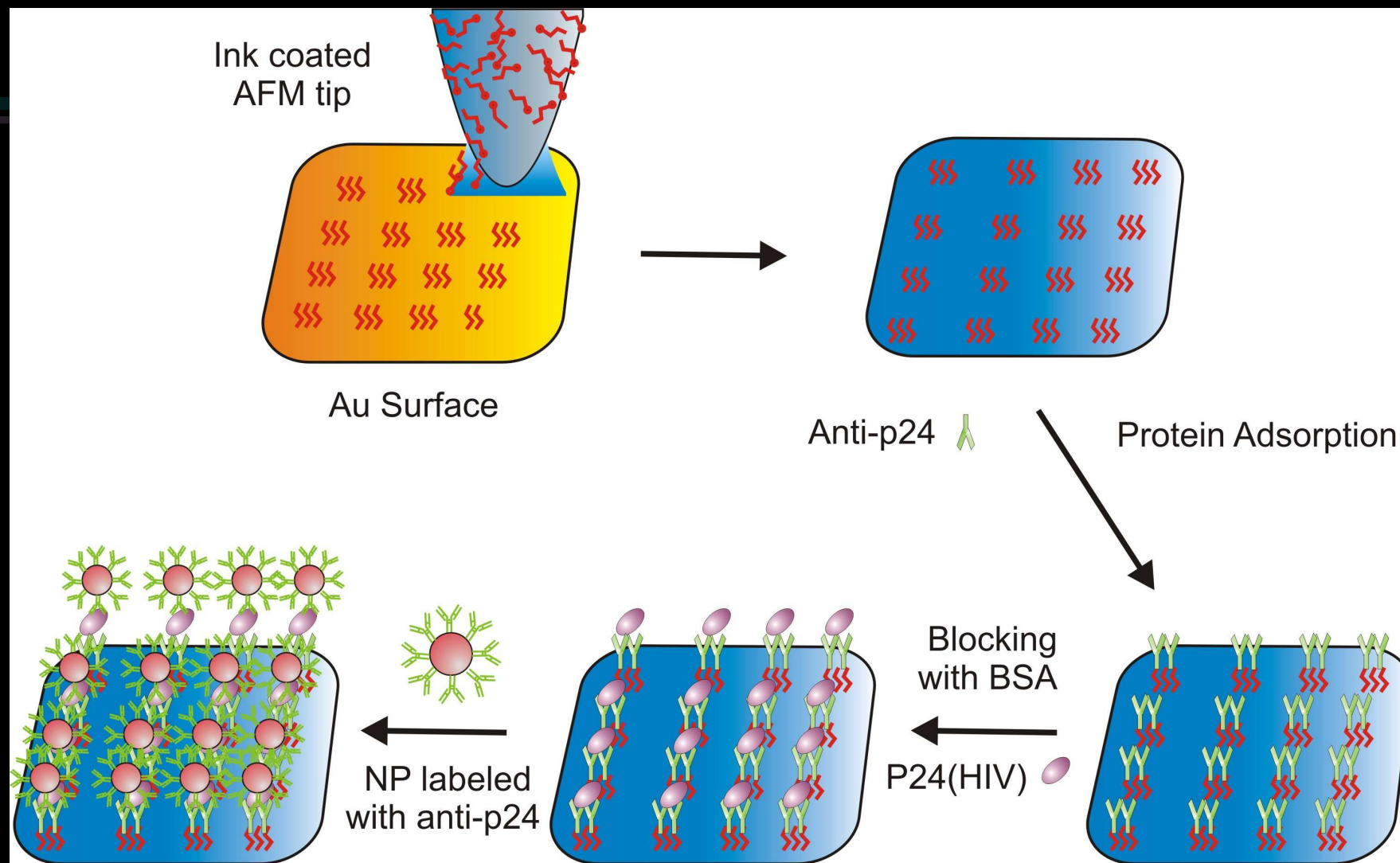
The Millipede chip: showing electrical wiring for 1,024 tips etched out in a 3x3mm square.

Biomolecular Nanoarrays via Direct-Write DPN



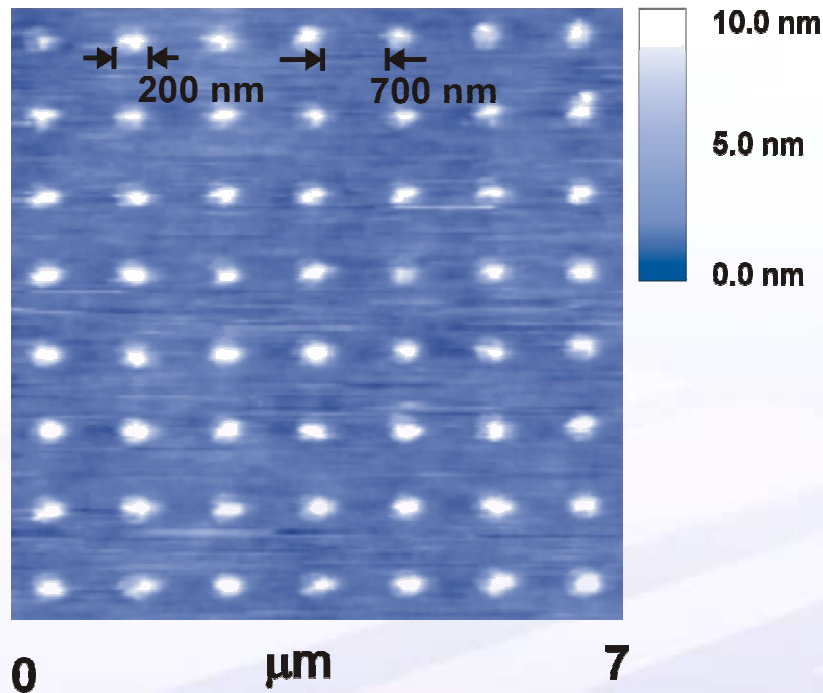
- More than just miniaturization with higher density
- New opportunities for biodetection and studying biorecognition
- Small sample volumes required
- Higher sensitivity
- New readout capabilities (eg. probeless detection)

Nanoarrays for Antigen-Based Detection of HIV

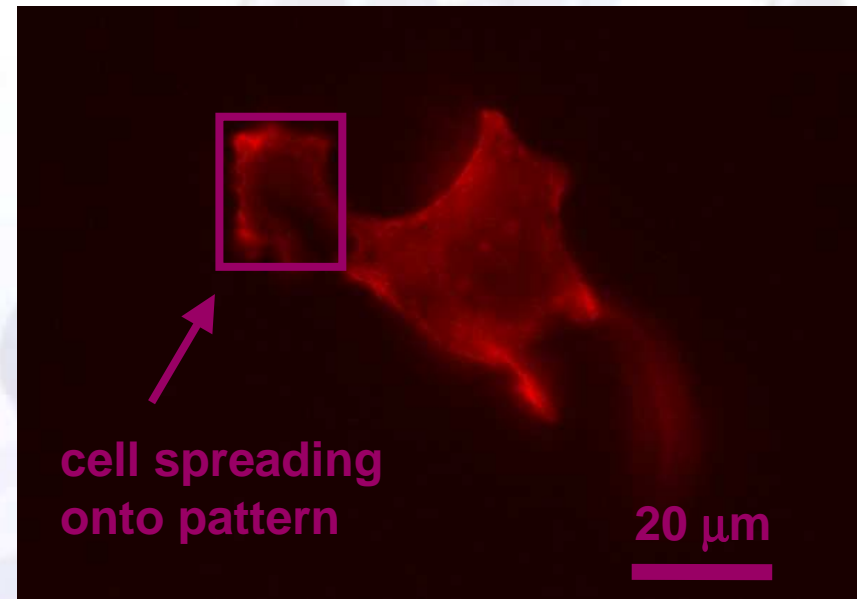


Protein Nanoarrays for Cell Adhesion Studies

DPN arrays of Retronectin
(AFM topography)



Fluorescence Micrograph of Cell Spreading onto DPN Pattern



with J. C. Smith and M. Mrksich at U. of Chicago

Lee, K.-B. *Science* 295, 1702 (2002).

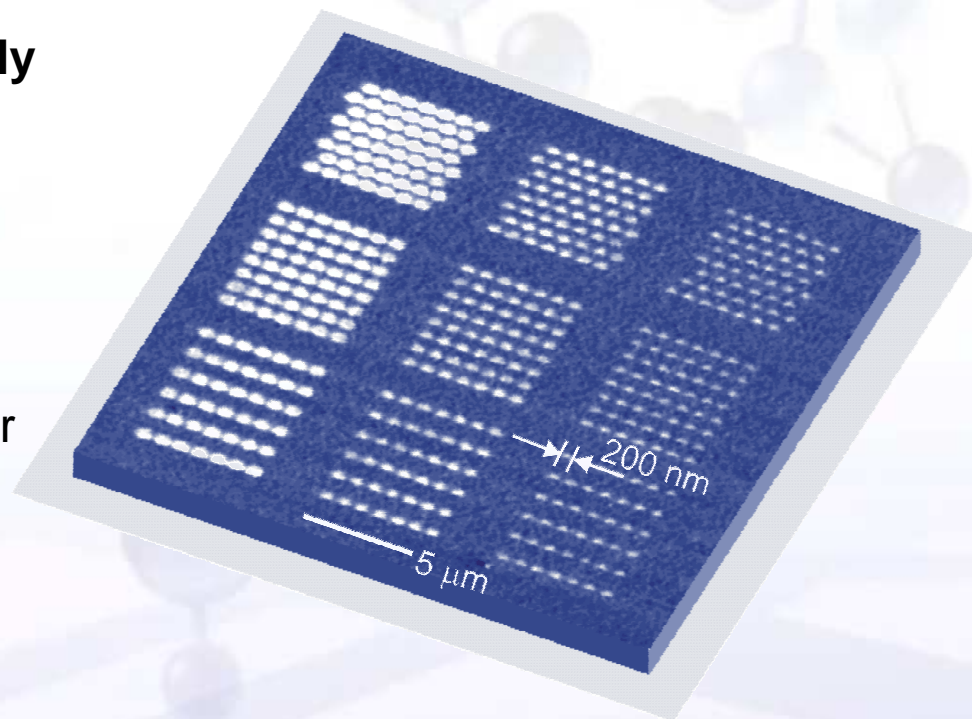
Combinatorial DPN

DPN enables one to systematically vary lattice parameters...

- Composition
- Spacing
- Dot size
- Orientation

Applications...

- Magnetic, metallic, and polymer nanoparticle assembly
- Colloidal crystallization
- Catalysis
- Cell adhesion studies
- Photonic materials
- Combinatorial synthesis of materials and biomolecules (DNA, peptides)



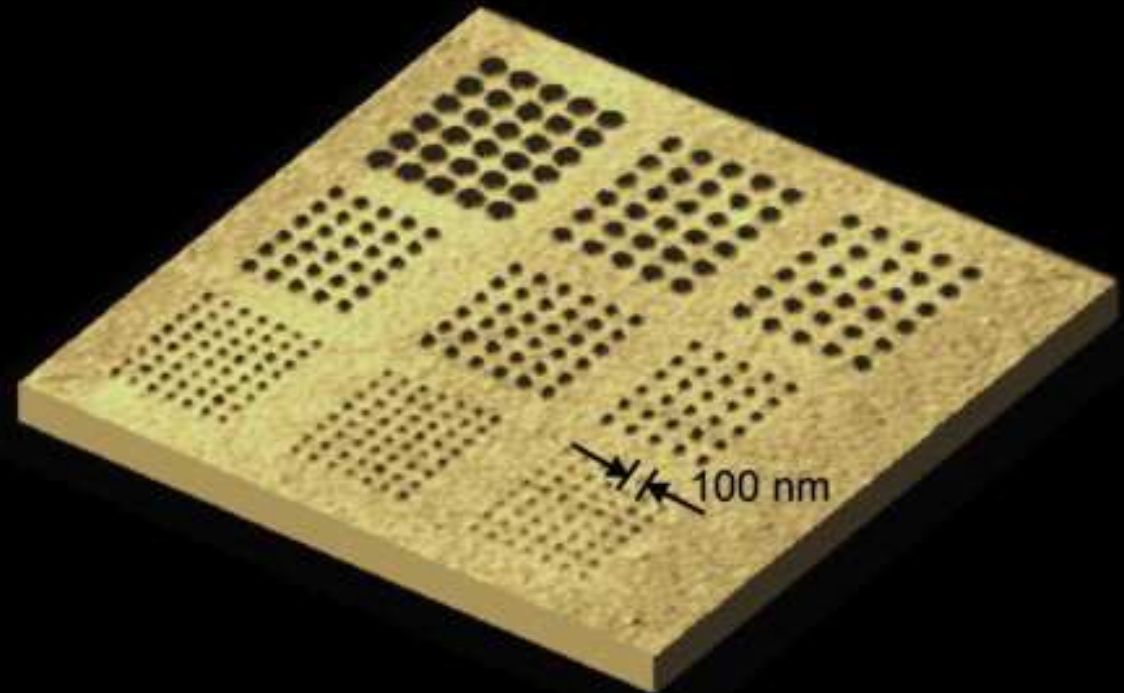
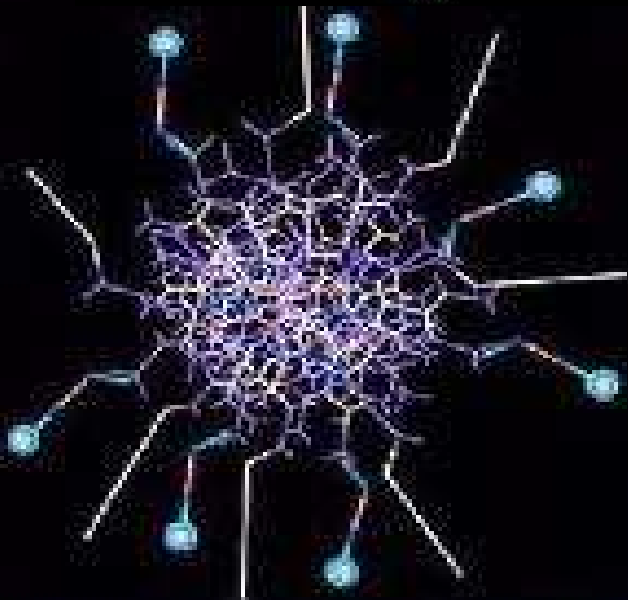
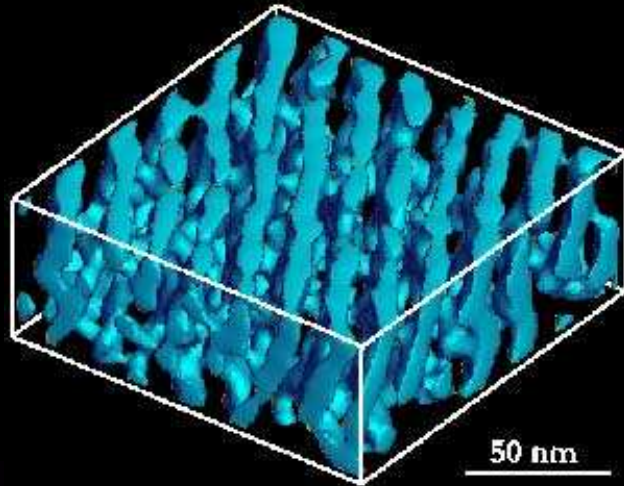
LFM Image of DPN-generated template on Au of 16-mercaptohexadecanoic acid for assembly of (+)charged particles

Demers, L. M. et al *Angew. Chem.* 40, 3069 (2001).

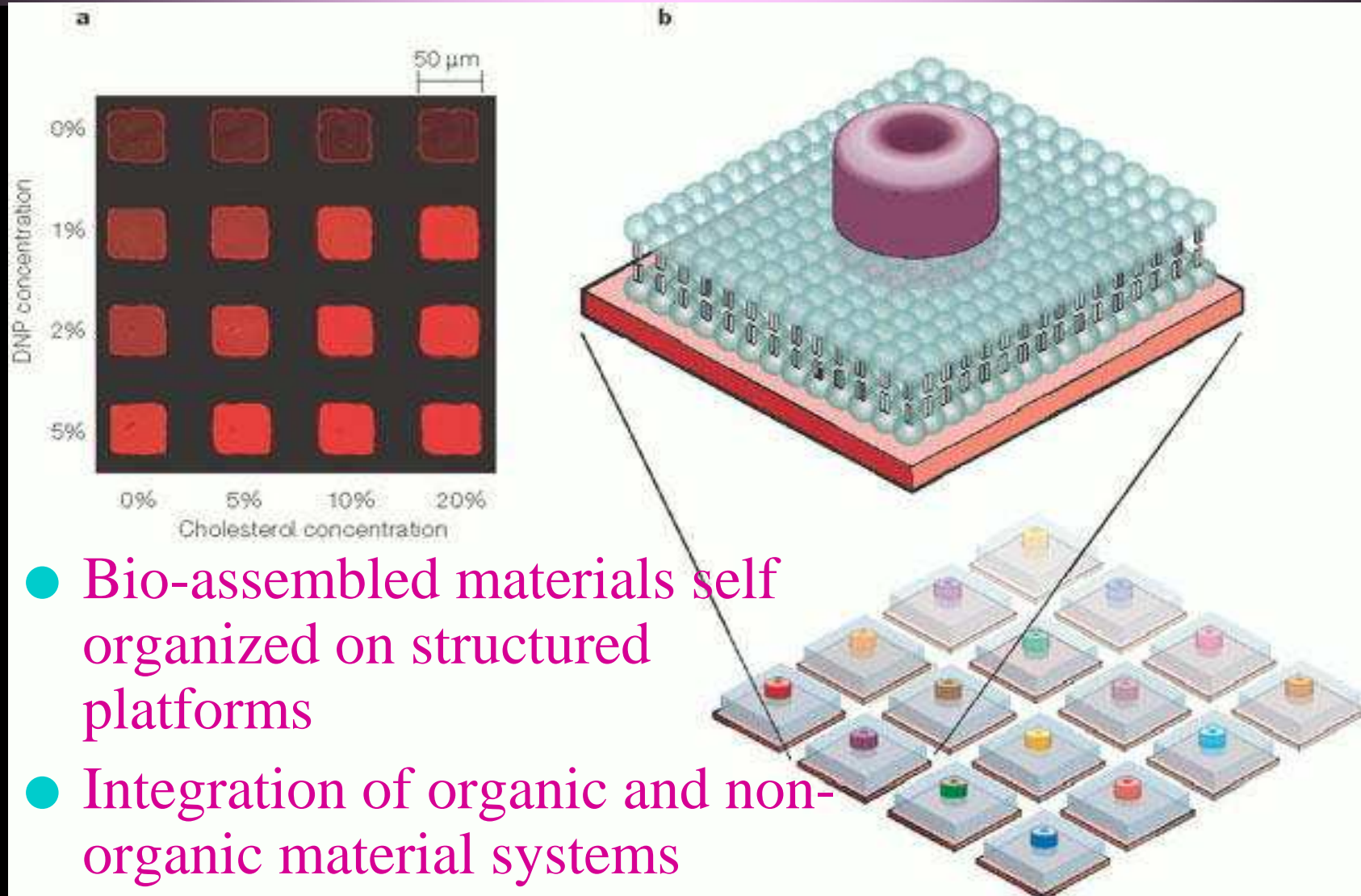


get small™

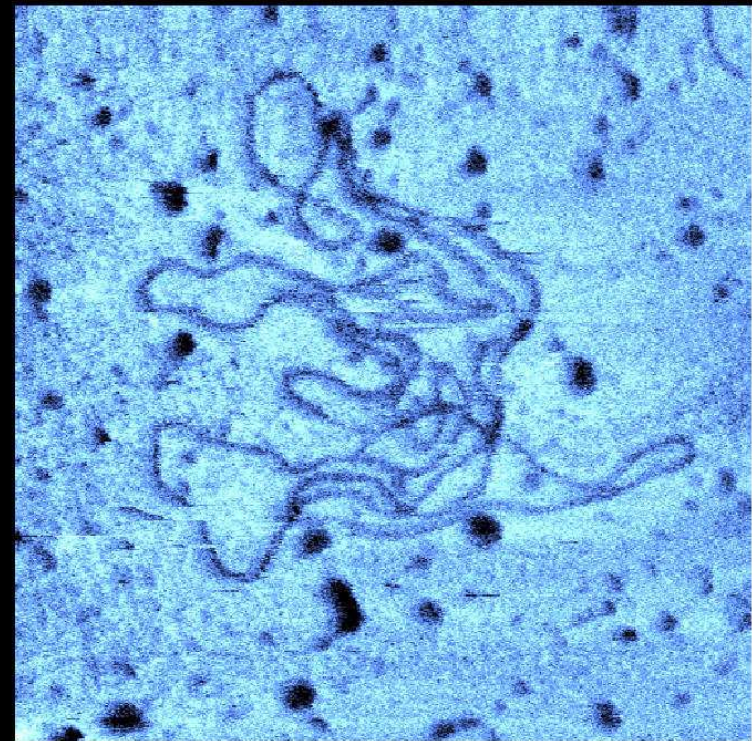
Diversity of Tools – Integration of “traditional” and biologically enabled or inspired processes and materials



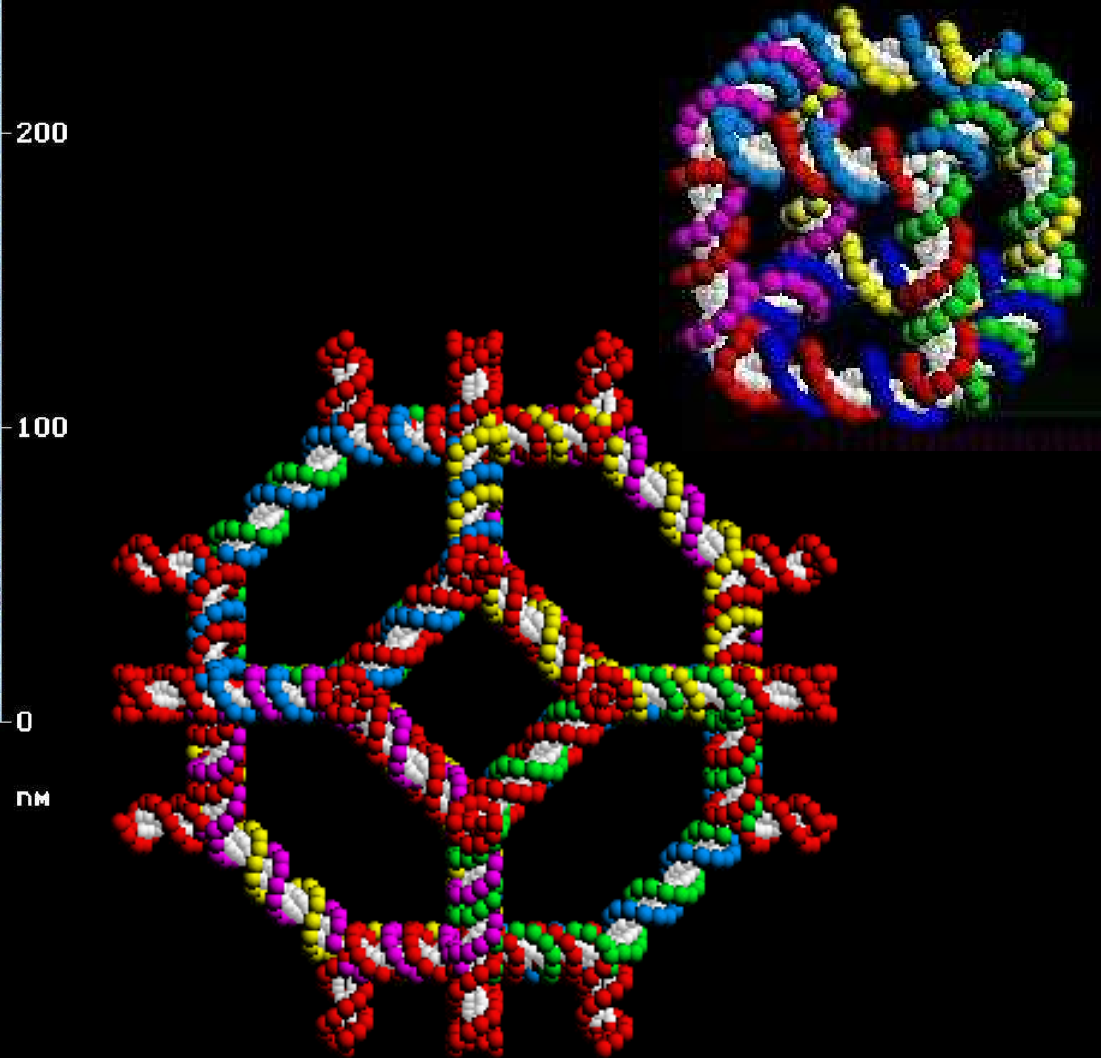
Integrated Biofoundry Processes



Structural Proteomics - Proteomic Assembly

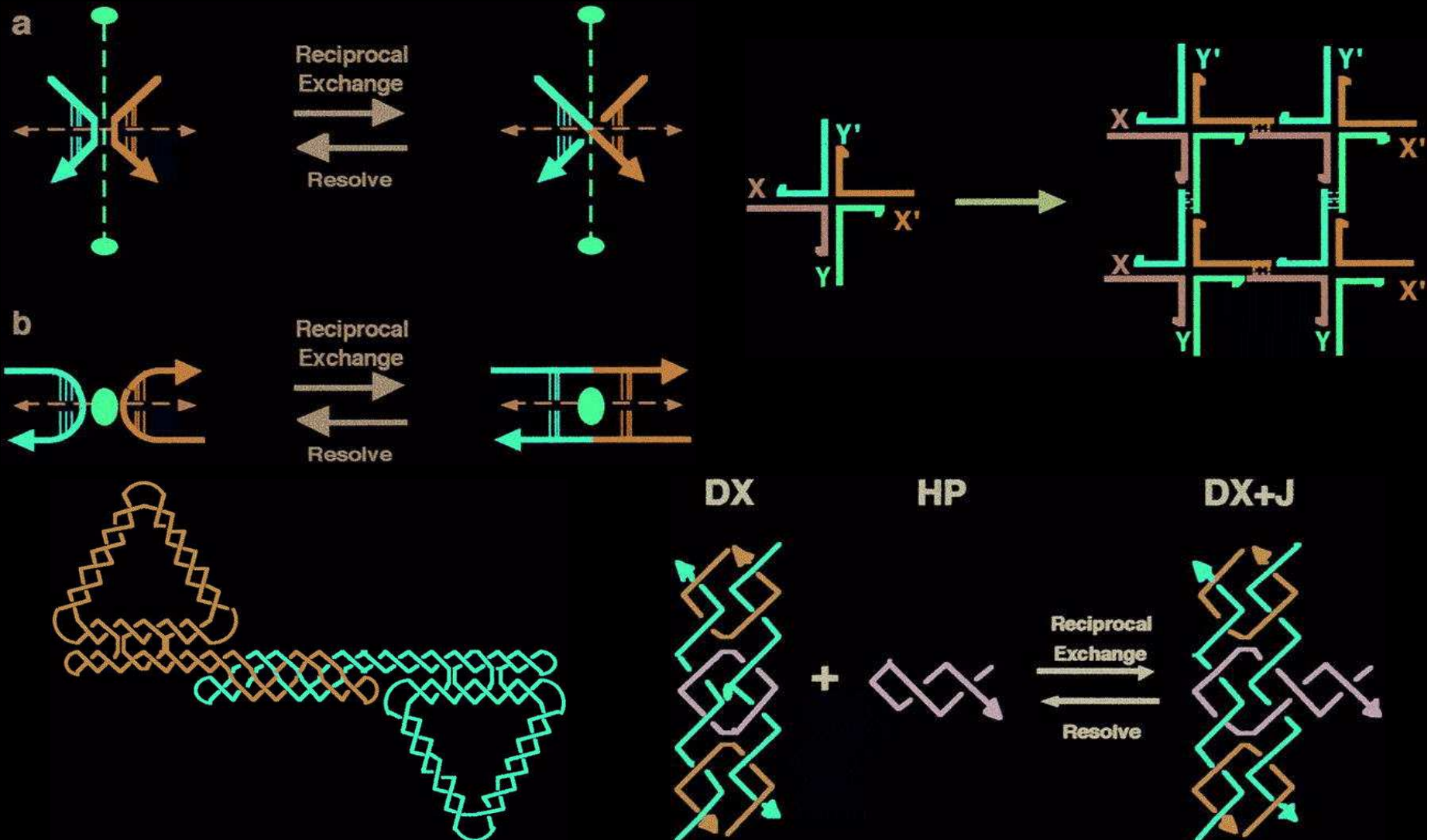


0 100 200
nm

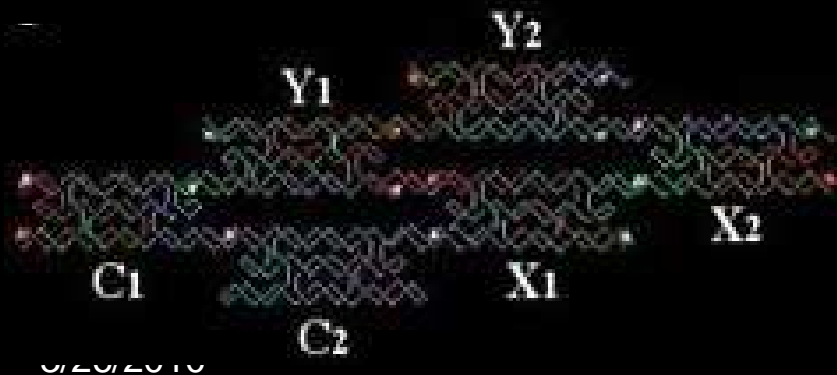
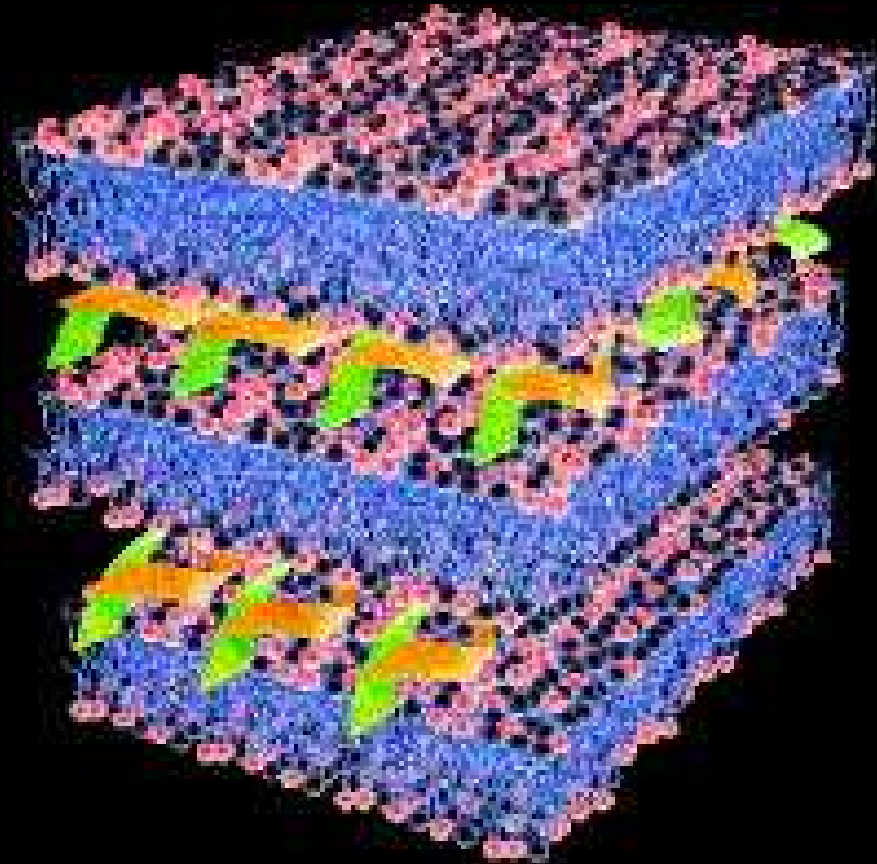


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Structural Proteomics - Proteomic Assembly



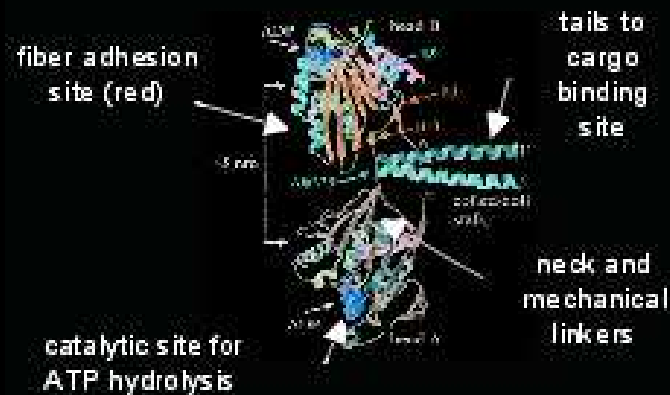
Structural Proteomics - Proteomic Assembly



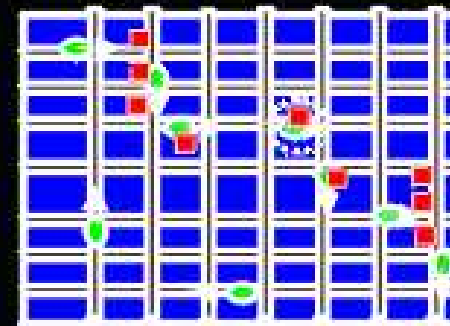
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Structural Proteomics - Proteomic Assembly

Modify Proteins



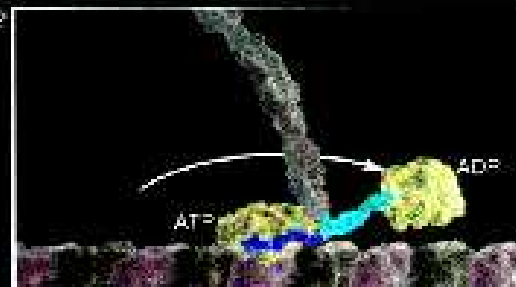
Assemble Fiber Networks



Monitor Protein Function



Activate Proteins



Combinatorial / Synergistically Inter-relatable Process Modalities

- Self-assembled DNA /
carbon nanotube
“nanobiotronic”
devices

U of South Carolina -
Seminario, Agapito,
Figueroa

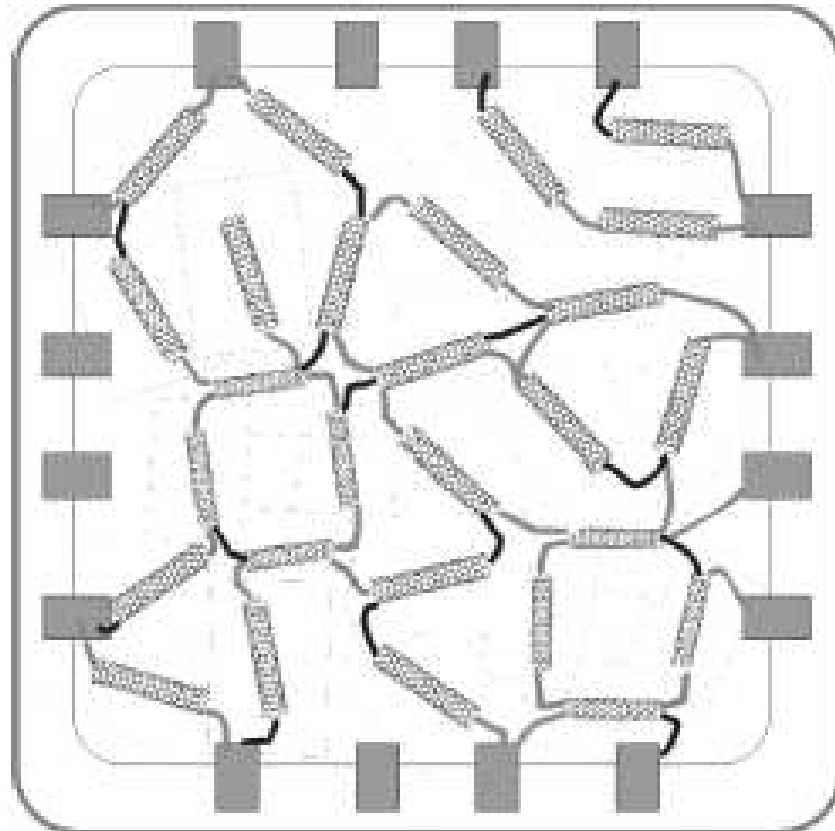


Fig. 1. A bionanochip, based in polygons made of carbon nanotubes and interconnecting DNA fragments.

Process Dynamics of the Evolutionary Eventstream

Designed Evolution Restoration & Healing Augmentation



Present

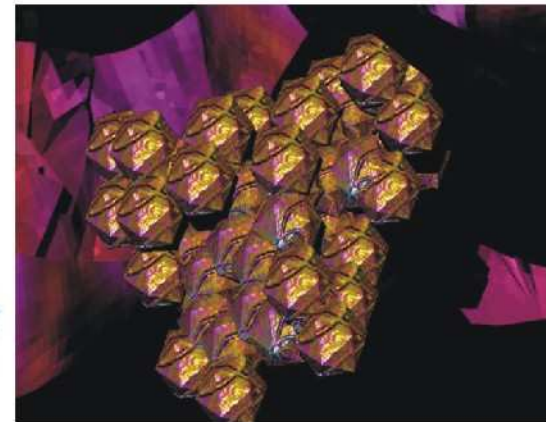
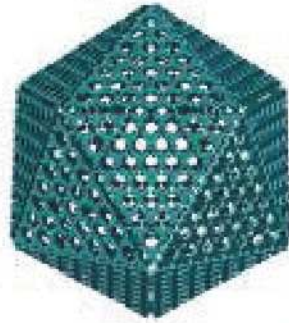
Transition

Future

Augmentation

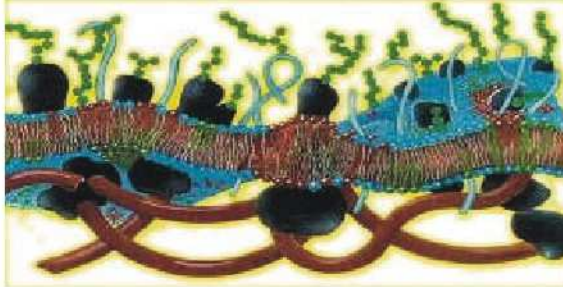
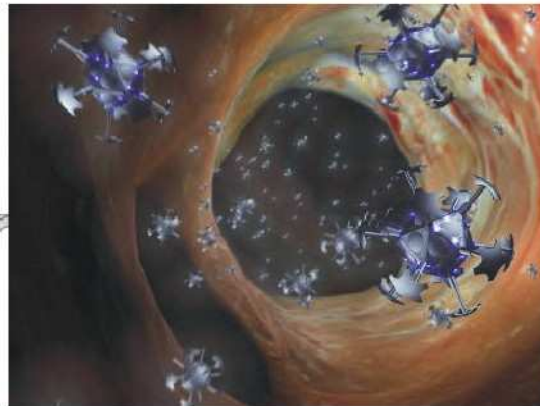
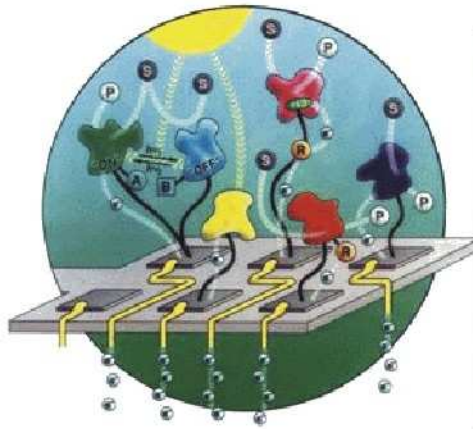
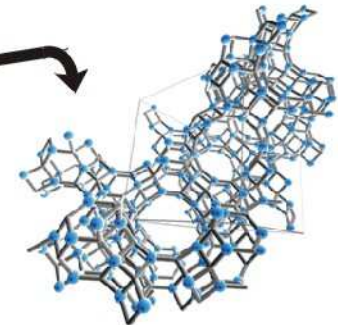
Cognition Enhancement
Physical Enhancement

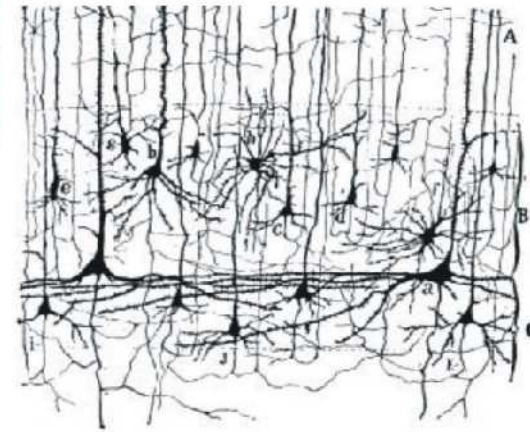
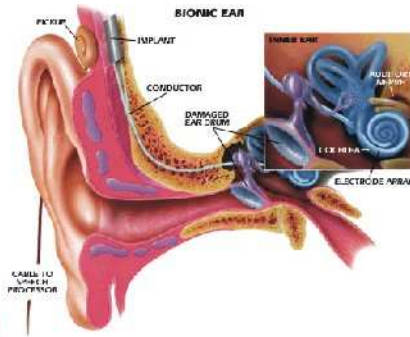
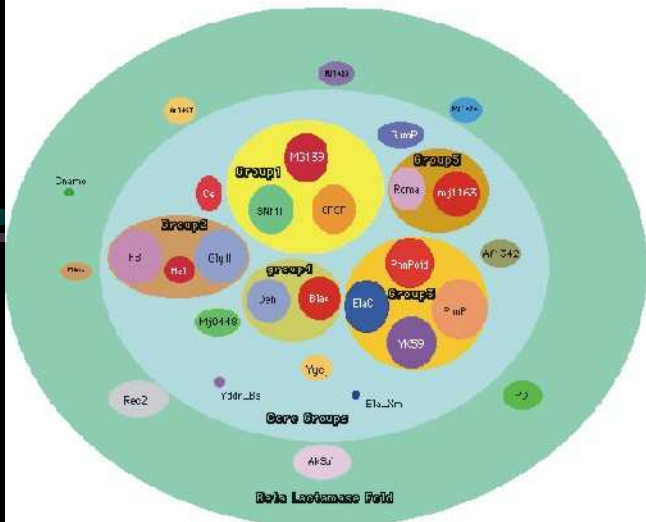
Parallel Processing Capacity
Complexity Management
Extended Life Productivity



Scenario:
Synthetic Nano-Organisms
Xenomorph Hunter/Killer Biobots
Hypervirulent Proteomic Targeting

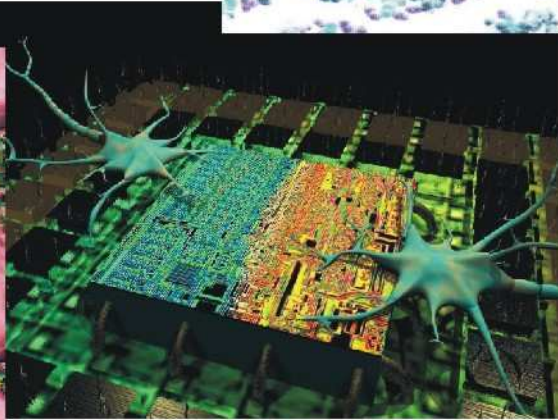
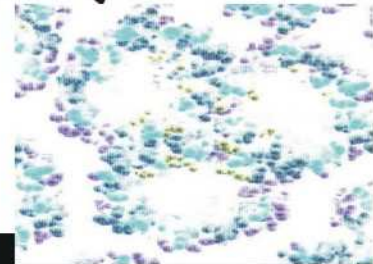
Response:
"Smart" nano-defensive skin /
molecular neutralization
Synthetic immune system "patrol nanites"
Nano-bio sensor implants





Scenario:
 Extended sensory capacities
 Extreme "hardened" endurance
 Enhanced performance

Solution:
 Nano-enhanced tissue
 "Smart" healing nano devices
 Biochip / integrated implants
 Neuro-prosthetics



Infotech / Biotech / Nanotech Convergence

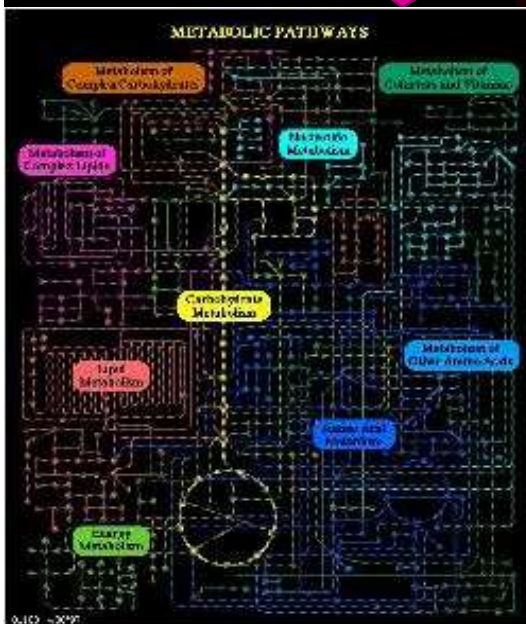
Think Different > Think Holographic

Biological Metaphors in Computing

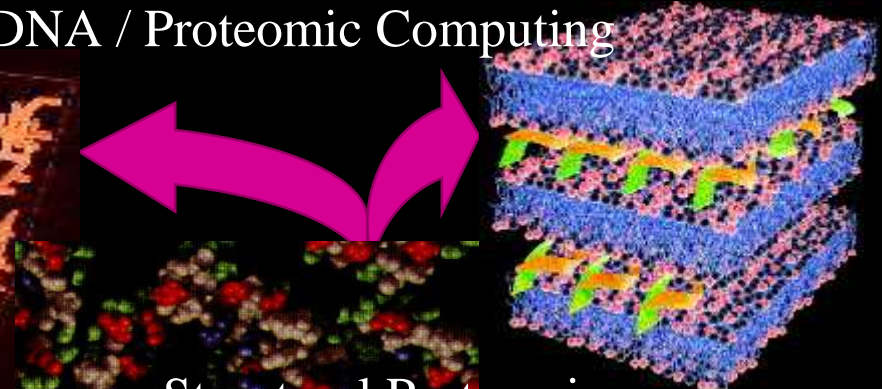
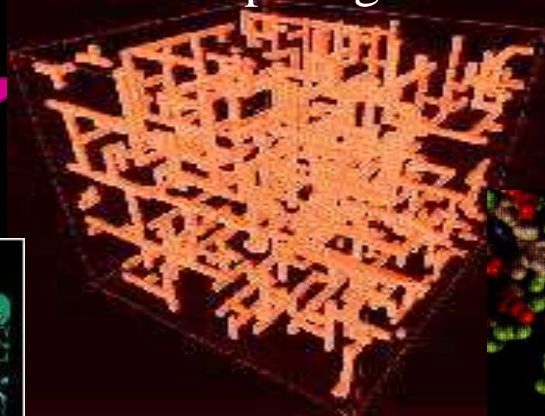
DNA / Proteomic Computing

Bioinformatics

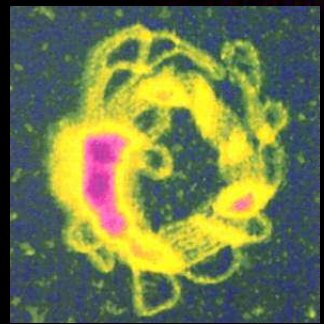
In Silico Biology



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Structural Proteomics



Genetic / BioMed Proteomics

Nano Electronics & Photonics Forum

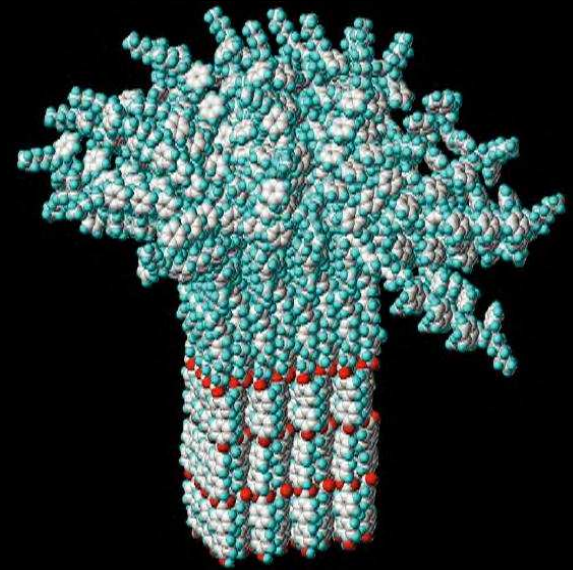


Nano Electronics
& Photonics Forum

Conference Oct 26, 2004, Palo Alto

www.NanoSIG.org/nanoelectronics.htm

Our mission is to provide our members and sponsors with a key competitive advantage in the next industrial revolution spawned by the convergence of interrelated domains of applied nanotechnology in electronics and photonics.



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