*Manufacturing Solutions for Digital Healthcare with BIGHEART**

**Bionanoscience for Innovative Global Healthcare Research & Technology*

Luke P. Lee

Arnold and Barbara Silverman Distinguished Professor

Bioengineering, Electrical Engineering & Computer Science, and Biophysics

Greetings from

BioPOETS

Bioinspired

Photonics

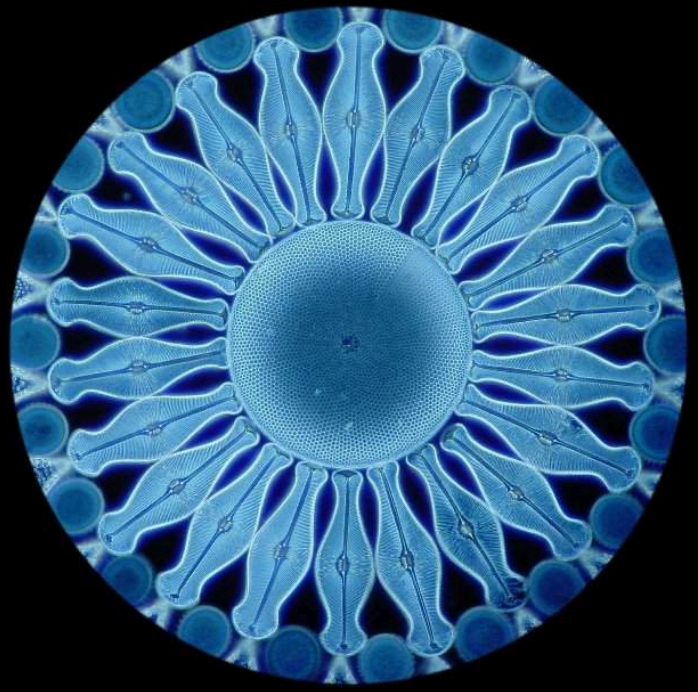
Optofluidics

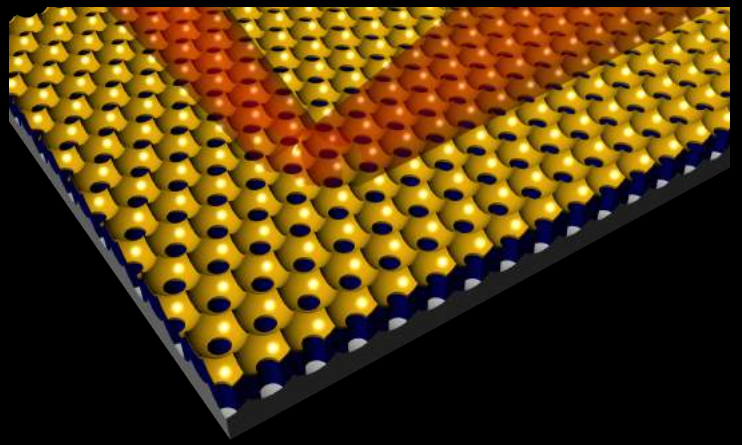
Electronics

Technology &

Science

Fiat Lux!





Auguries of Innocence

To see a world in a grain of sand
And a heaven in a wild flower,
Hold infinity in the palm of your hand,
And eternity in an hour.

A robin redbreast in a cage
Puts all heaven in a rage.

A dove-house fill'd with doves and pigeons
Shudders hell thro' all its regions.
A dog starv'd at his master's gate
Predicts the ruin of the state.

A horse misused upon the road
Calls to heaven for human blood.
Each outcry of the hunted hare
A fibre from the brain does tear.

A skylark wounded in the wing,
A cherubim does cease to sing.
The game-cock clipt and arm'd for fight
Does the rising sun affright.

Every wolf's and lion's howl
Raises from hell a human soul.

The wild deer, wand'ring here and there,
Keeps the human soul from care.
The lamb misus'd breeds public strife,
And yet forgives the butcher's knife.

The bat that flits at close of eve
Has left the brain that won't believe.
The owl that calls upon the night
Speaks the unbeliever's fright.

He who shall hurt the little wren
Shall never be beloved by men.
He who the ox to wrath has mov'd
Shall never be by woman lov'd.

The wanton boy that kills the fly
Shall feel the spider's enmity.
He who torments the chafer's sprite
Weaves a bower in endless night.

The catterpillar on the leaf
Repeats to thee thy mother's grief.
Kill not the moth nor butterfly,
For the last judgment draweth nigh.

He who shall train the horse to war
Shall never pass the polar bar.
The beggar's dog and widow's cat,
Feed them and thou wilt grow fat.

The gnat that sings his summer's song
Poison gets from slander's tongue.
The poison of the snake and newt
Is the sweat of envy's foot.

The poison of the honey bee
Is the artist's jealousy.

The prince's robes and beggar's rags
Are toadstools on the miser's bags.
A truth that's told with bad intent
Beats all the lies you can invent.

It is right it should be so;
Man was made for joy and woe;
And when this we rightly know,
Thro' the world we safely go.

Joy and woe are woven fine,
A clothing for the soul divine.
Under every grief and pine
Runs a joy with silken twine.

The babe is more than swaddling bands;
Throughout all these human lands;
Tools were made and born were hands,
Every farmer understands.
Every tear from every eye
Becomes a babe in eternity;

This is caught by females bright,
And return'd to its own delight.
The bleat, the bark, bellow, and roar,
Are waves that beat on heaven's shore.

The babe that weeps the rod beneath
Writes revenge in realms of death.
The beggar's rags, fluttering in air,
Does to rags the heavens tear.

The soldier, arm'd with sword and gun,
Palsied strikes the summer's sun.
The poor man's farthing is worth more
Than all the gold on Afric's shore.

One mite wrung from the lab'rer's hands
Shall buy and sell the miser's lands;
Or if protected from on high,
Does that whole nation sell and buy.

He who mocks the infant's faith
Shall be mock'd in age and death.
He who shall teach the child to doubt
The rotting grave shall ne'er get out.

He who respects the infant's faith
Triumphs over hell and death.
The child's toys and the old man's reasons
Are the fruits of the two seasons.

The questioner, who sits so sly,
Shall never know how to reply.
He who replies to words of doubt
Doth put the light of knowledge out.

The strongest poison ever known
Came from Caesar's laurel crown.
Nought can deform the human race
Like to the armour's iron brace.

When gold and gems adorn the plow,
To peaceful arts shall envy bow.
A riddle, or the cricket's cry,
Is to double a fit reply.

The emmet's inch and eagle's mile
Make lame philosophy to smile.
He who doubts from what he sees
Will ne'er believe, do what you please.

If the sun and moon should doubt,
They'd immediately go out.
To lie in a passion you good may do,
But no good if a passion is in you.

The whore and gambler, by the state
Licensed, build that nation's fate.
The harlot's cry from street to street
Shall weave old England's winding-sheet.

The winner's shout, the loser's curse,
Dance before dead England's hearse.

Every night and every morn
Some to misery are born,
Every morn and every night
Some are born to sweet delight.

Some are born to sweet delight,
Some are born to endless night.

We are led to believe a lie
When we see not thro' the eye,
Which was born in a night to perish in a night,
When the soul slept in beams of light.

God appears, and God is light,
To those poor souls who dwell in night;
But does a human form display
To those who dwell in realms of day.

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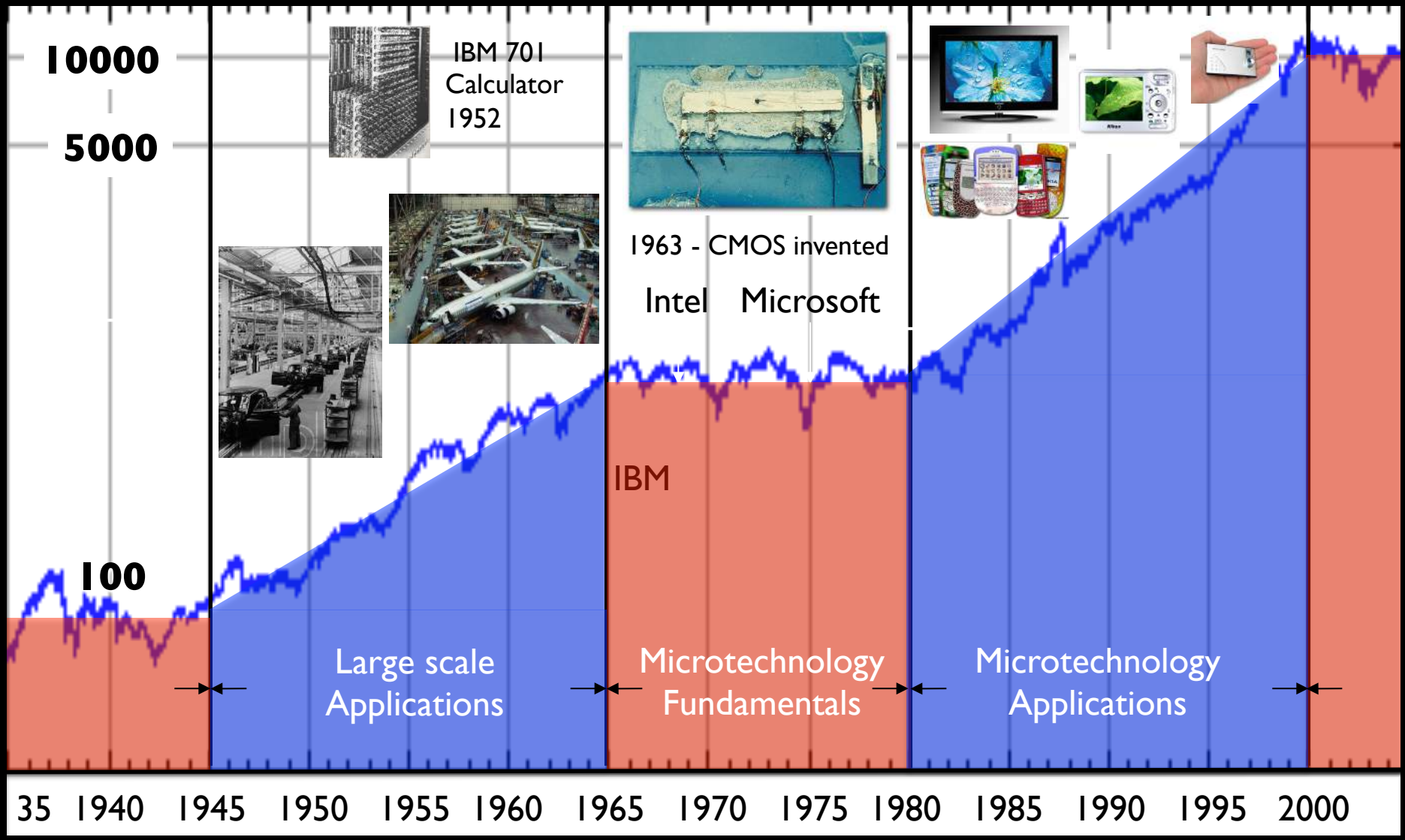
William Blake

Outline

- Motivations
  - *Solving global healthcare challenges with BIGHEART**
- Innovative Manufacturing for Personalized Medicine
  - *Integrated Molecular Diagnostic Systems (iMDx)*
  - *Integrative Microphysiological Analysis Platforms (iMAPs)*
  - *Quantum Nanoscope*
- Creativity in Precision Manufacturing in Healthcare
  - *Integrative Arts, Culture, Technology, and Science (iACTS)*
  - *Integrative Translational Engineering, Arts, Medicine, and Science (iTEAMS)*
- Summary

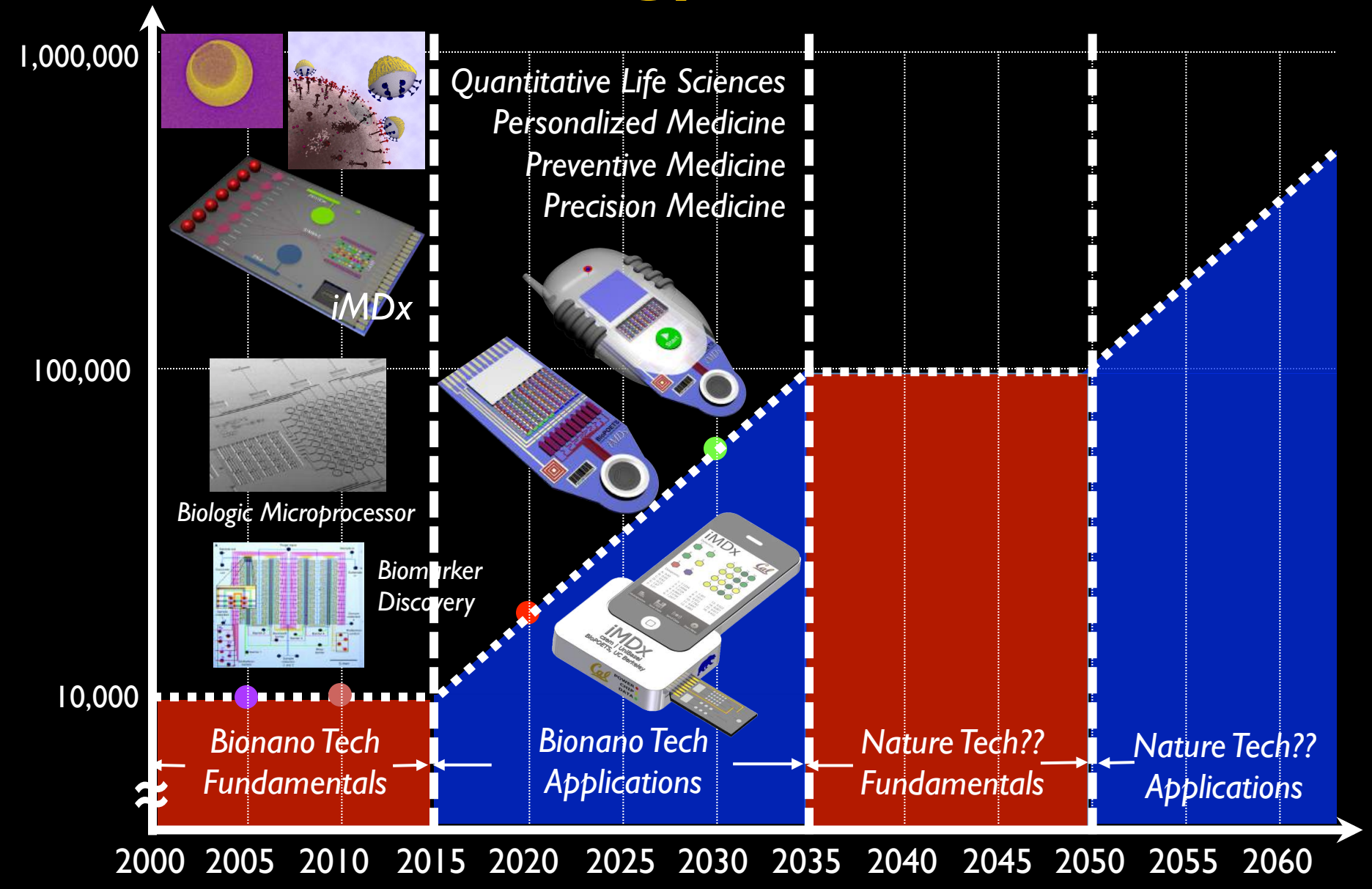
**Bionanoscience for Innovative Global Healthcare Research & Technology*

Dow Jones Industrial Index

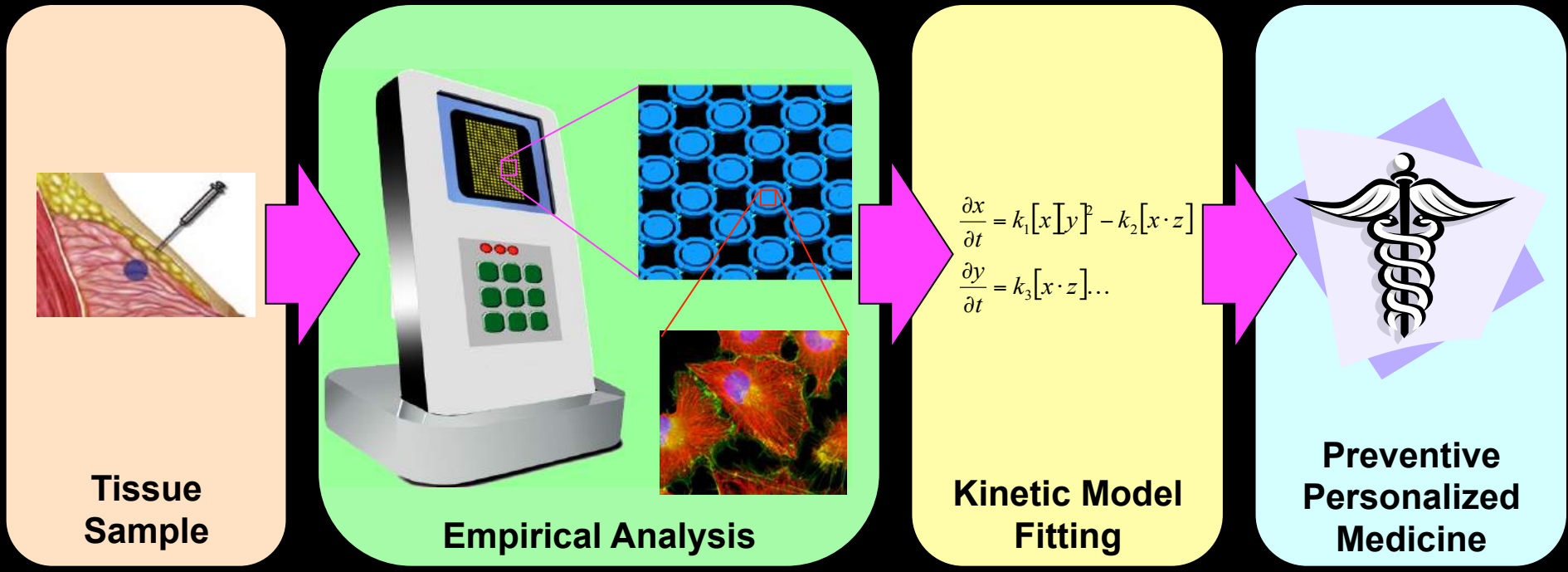


http://finance.yahoo.com

Technology, *Quo Vadis?*



Preventive Personalized Medicine

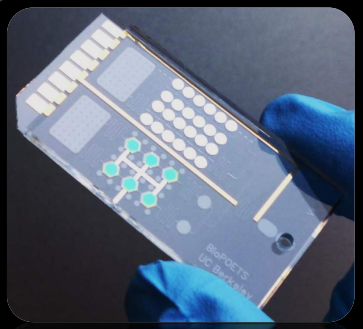


Fundamental Concepts:

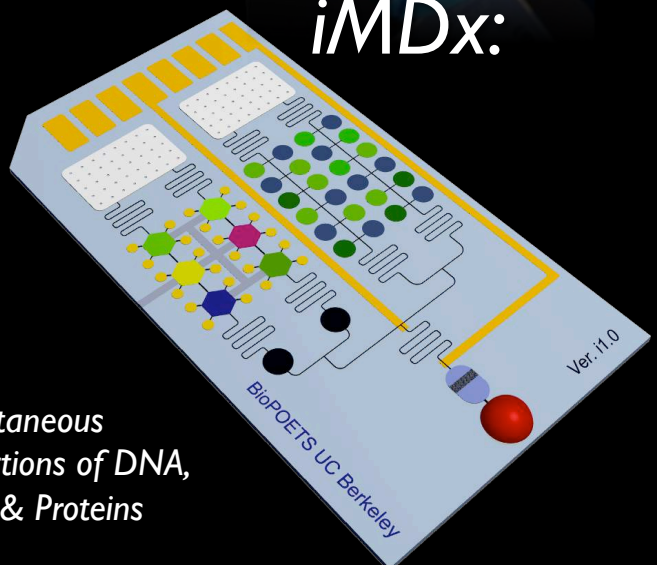
- Rapid collection of large experimental data sets
- Intelligent consolidation of quantitative values

Preventive
Personalized
Precision Medicine

New Medicine

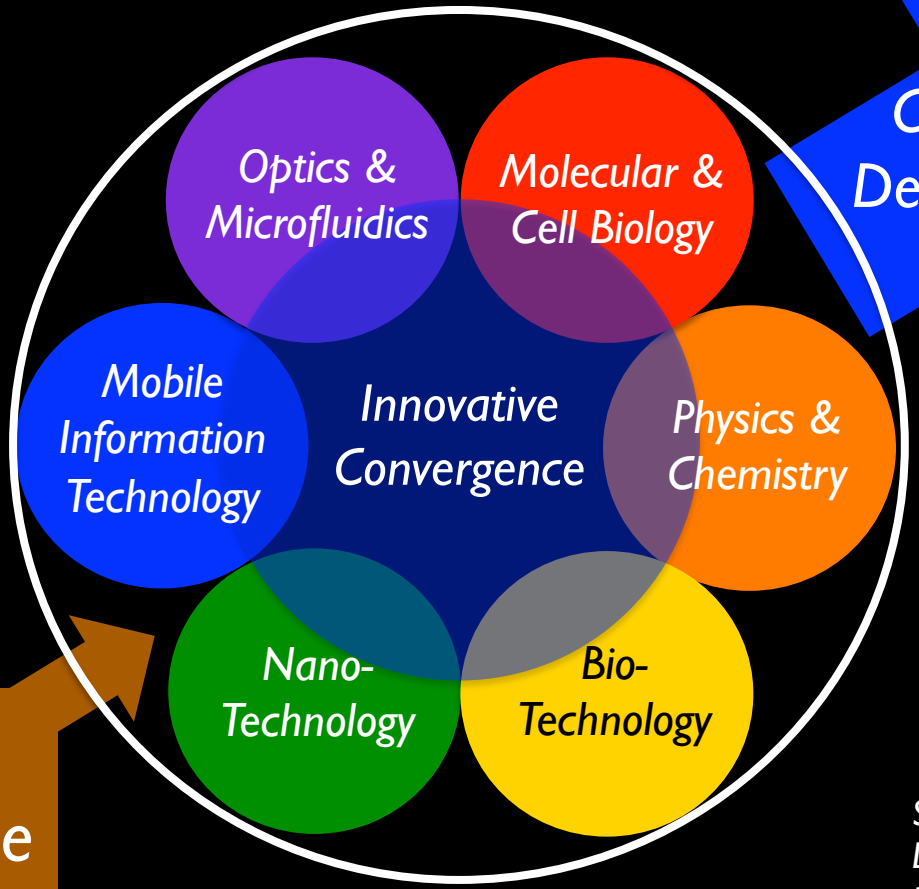


iMDx:



Simultaneous Detections of DNA, RNA, & Proteins

Creative Destruction



Old Medicine

Preventive Personalized Precision Medicine

New Medicine

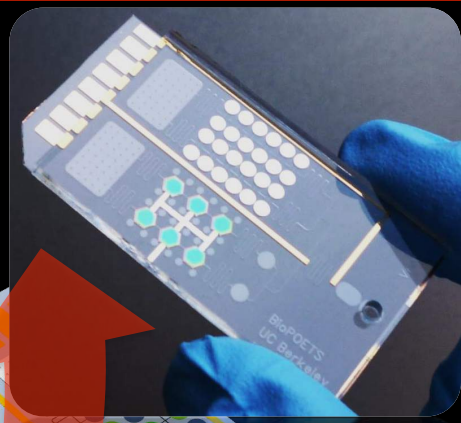
Creative Destruction

Requires

Innovative Precision Manufacturing

Optics & Microfluidics
Molecular & Cell Biology
Mobile Information Technology
Innovative Convergence
Physics & Chemistry
Nano-Technology
Bio-Technology

Old Medicine



iMDx:

Role of Precision Manufacturing

- Create jobs
- Establish healthy economy and healthy mind
- Create new sciences
  - *2014 Nobel Prizes in Chemistry (Microscope)*
  - *2014 Nobel Prizes in Physics (LED)*
- Become the best defense mechanism against global economic power
  - Global trade is based on goods, not services.
  - Services are dependent on manufactured goods.

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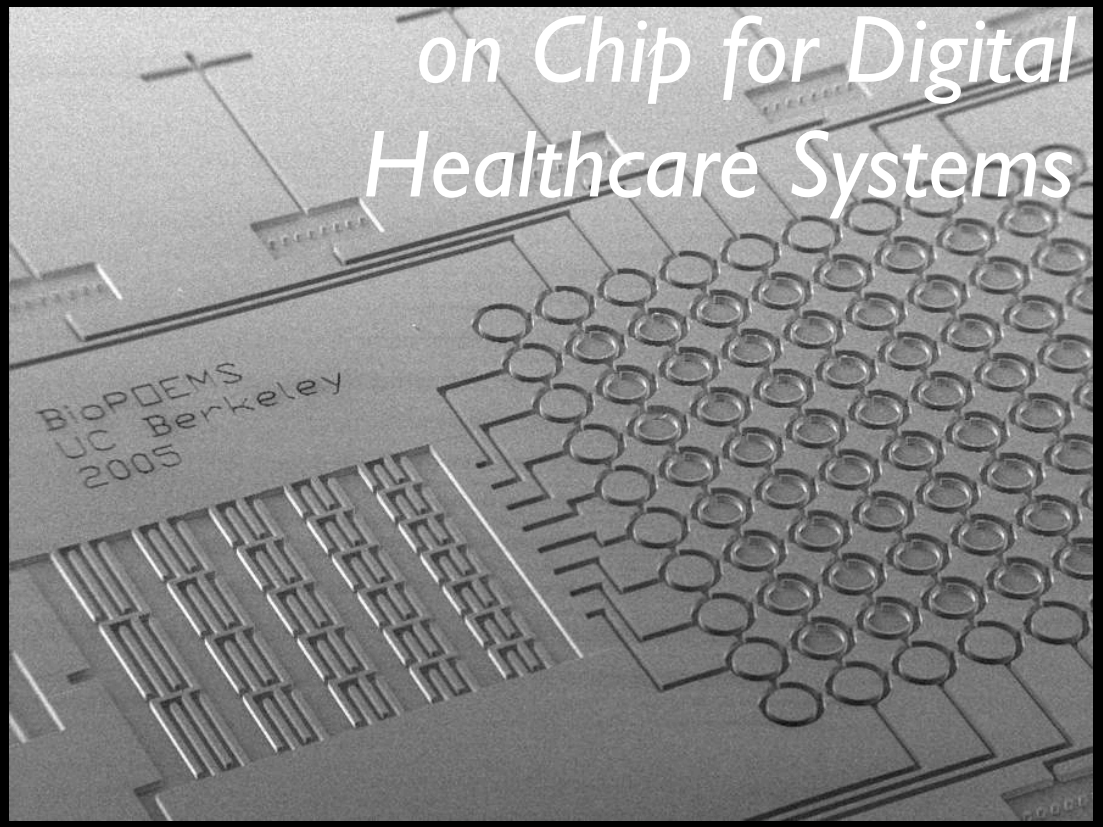
**Bionanoscience for Innovative Global Healthcare Research & Technology*

Innovative Additive Manufacturing for Personalized Medicine

BASICs for QB or not QB

Quantitative Biomedicine

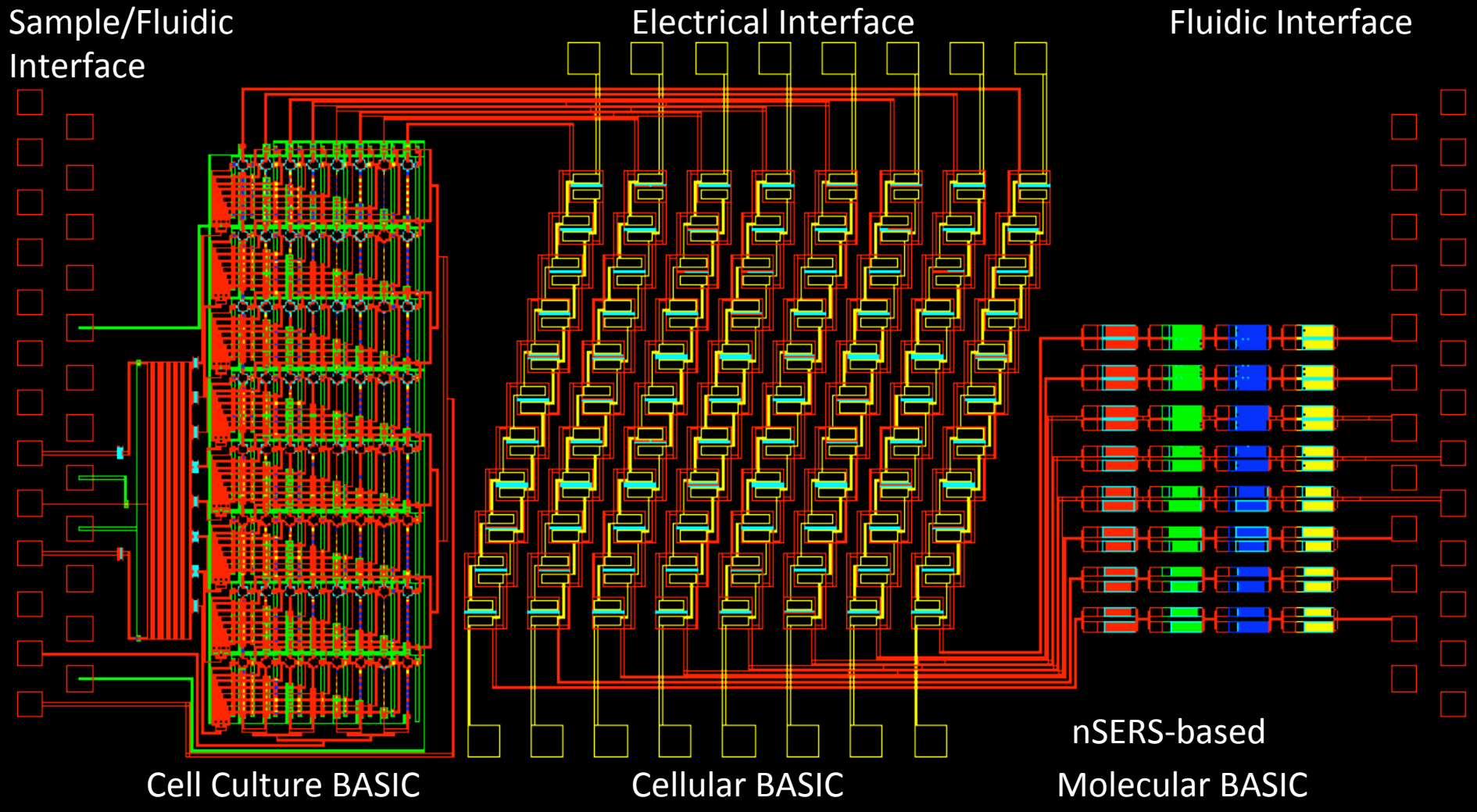
Biologic
Application
Specific
Integrated
Circuits



Simplicity
is the Ultimate
Sophistication

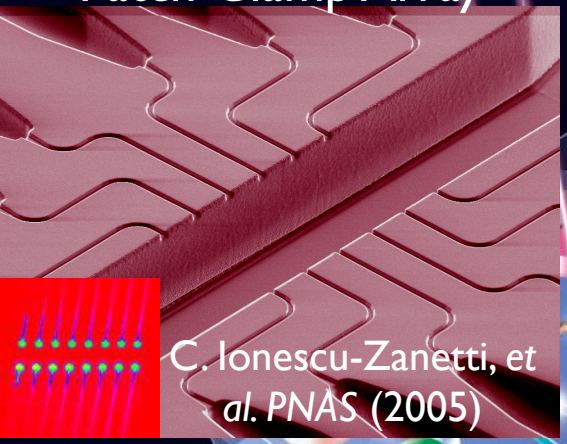
Leonardo da Vinci

Design Rule of BASICs



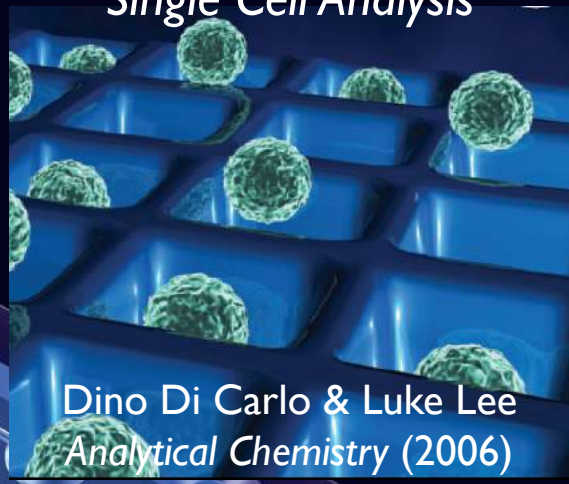
BASICs for Quantitative Biology

Patch Clamp Array



C. Ionescu-Zanetti, *et al. PNAS* (2005)

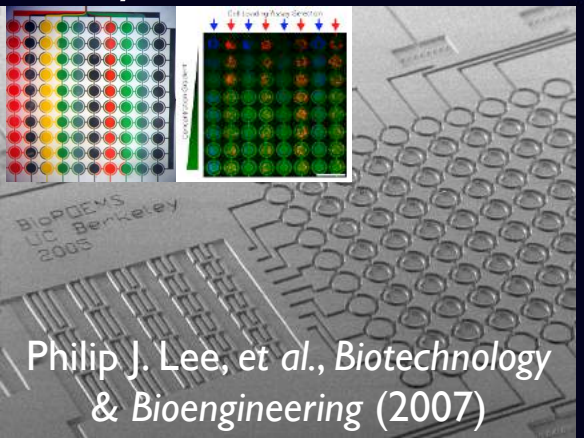
Single Cell Analysis



Dino Di Carlo & Luke Lee
Analytical Chemistry (2006)

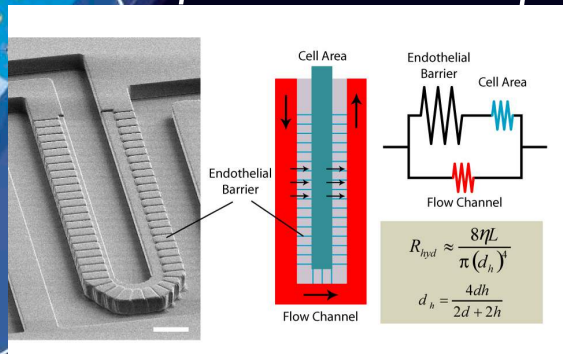
Gang L. Liu, *et al.*,
Nature Materials (2006)

Dynamic Cell Culture



Philip J. Lee, *et al.*, *Biotechnology & Bioengineering* (2007)

Artificial Liver on Chip



Lee *et al.*, Biotechnology & Bioengineering (2007)

- Lab-on-a-chip
- PoC Diagnostics
- Molecular Diagnostics

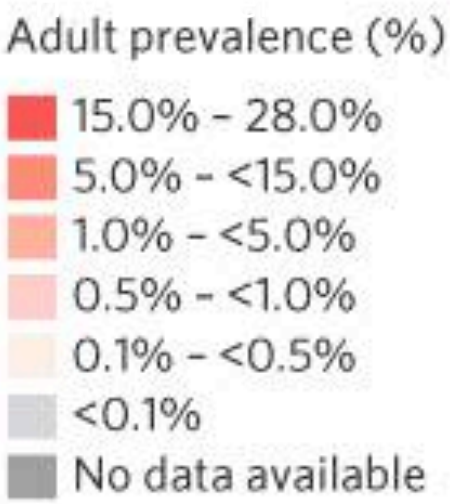
Integrated Molecular Diagnostics: *i*MDs *for Global Healthcare*

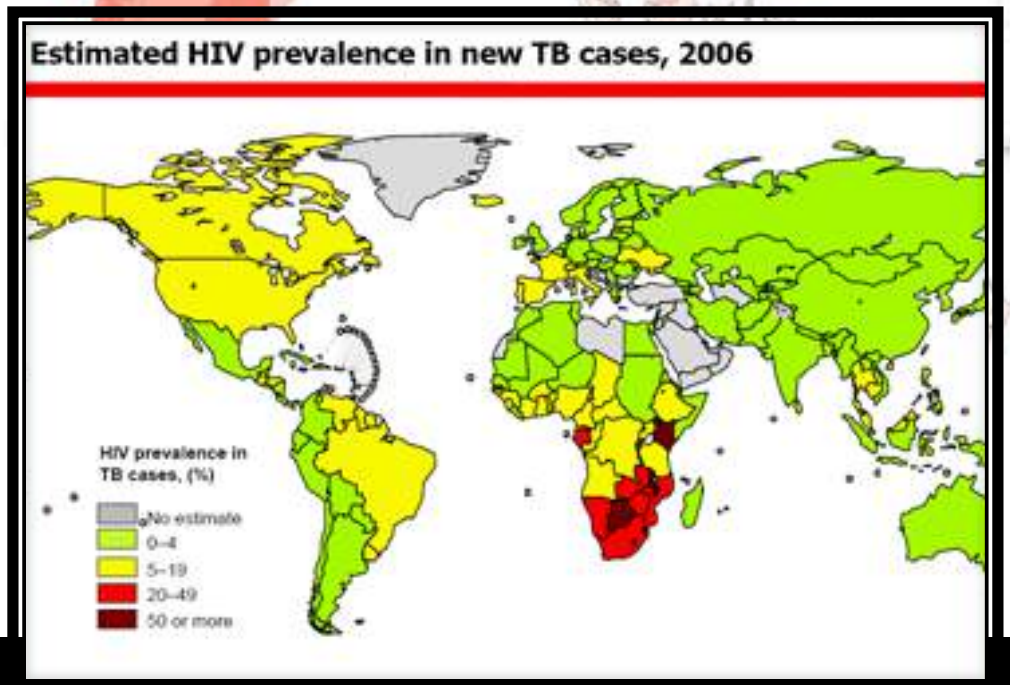
Emphasis:

"sample-to-answer" devices

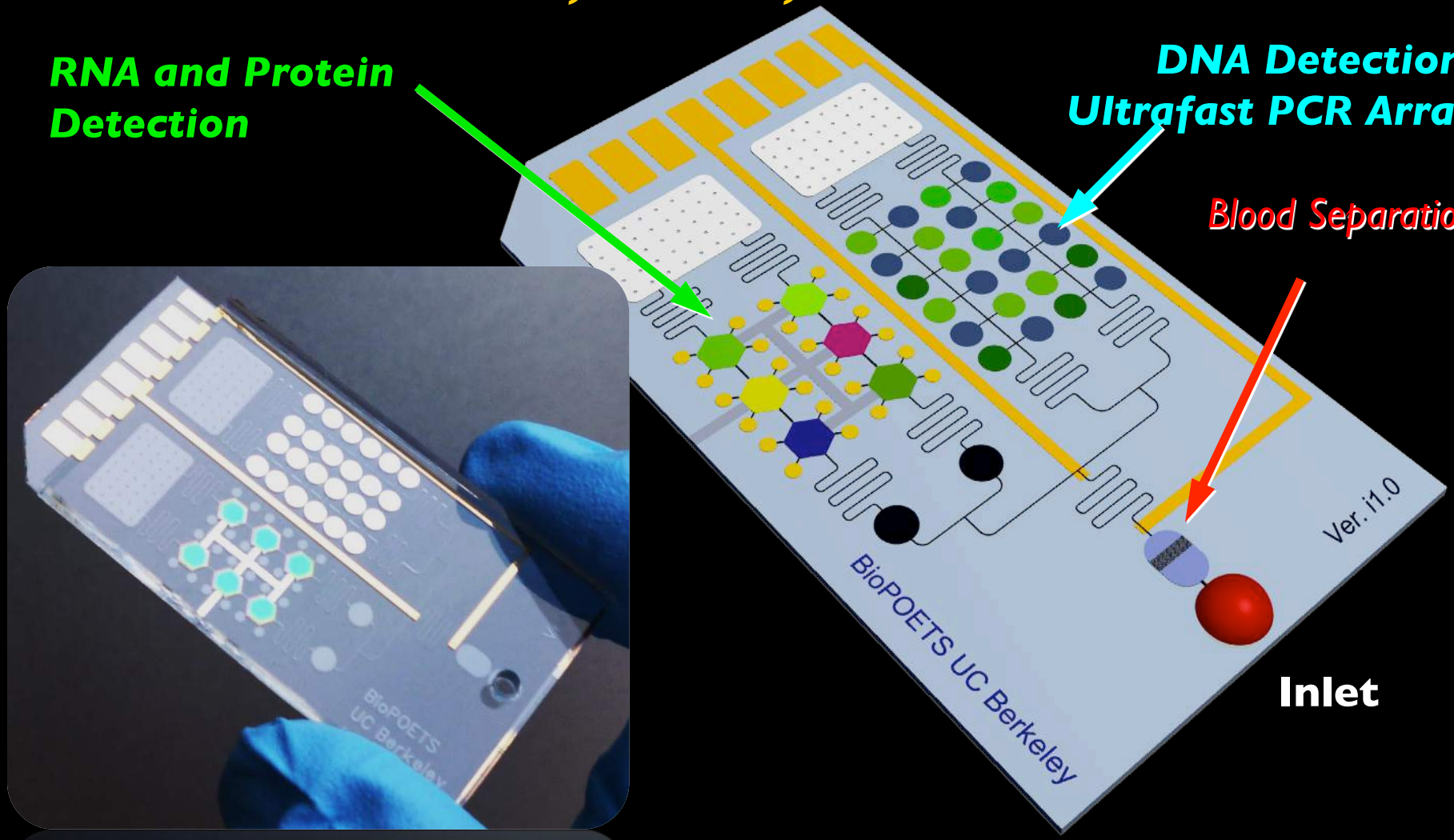
@ low cost

- HIV, TB, and many other infectious diseases are major burden for global healthcare
- HIV & TB have a synergistic interaction
- Combined (HIV & TB only) kill about 5 million people per year





iMDx: *Simultaneous Detection of DNAs, RNAs, & Proteins*



ASSURED iMDx

requires integrative multi-scale precision manufacturing

Affordable

Sensitive

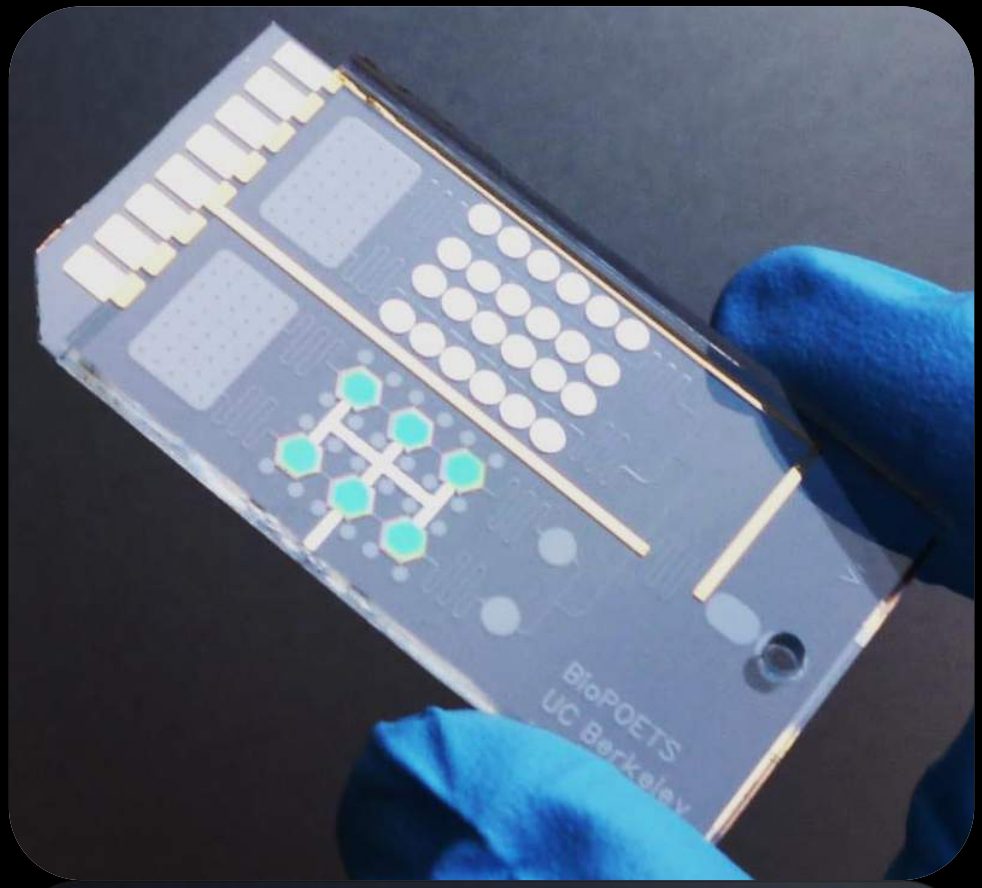
Specific

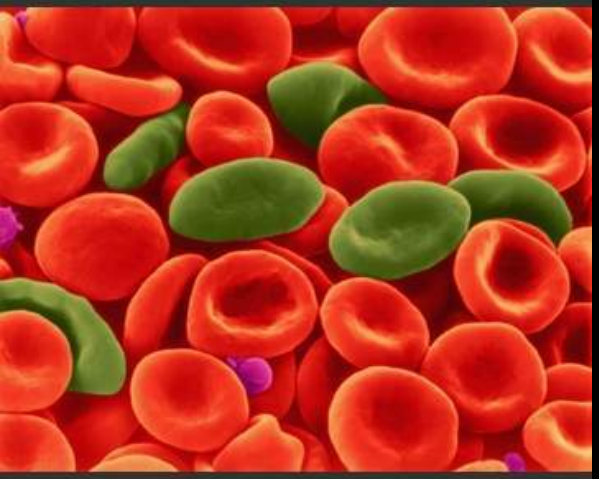
User-friendly

Robust/Rapid

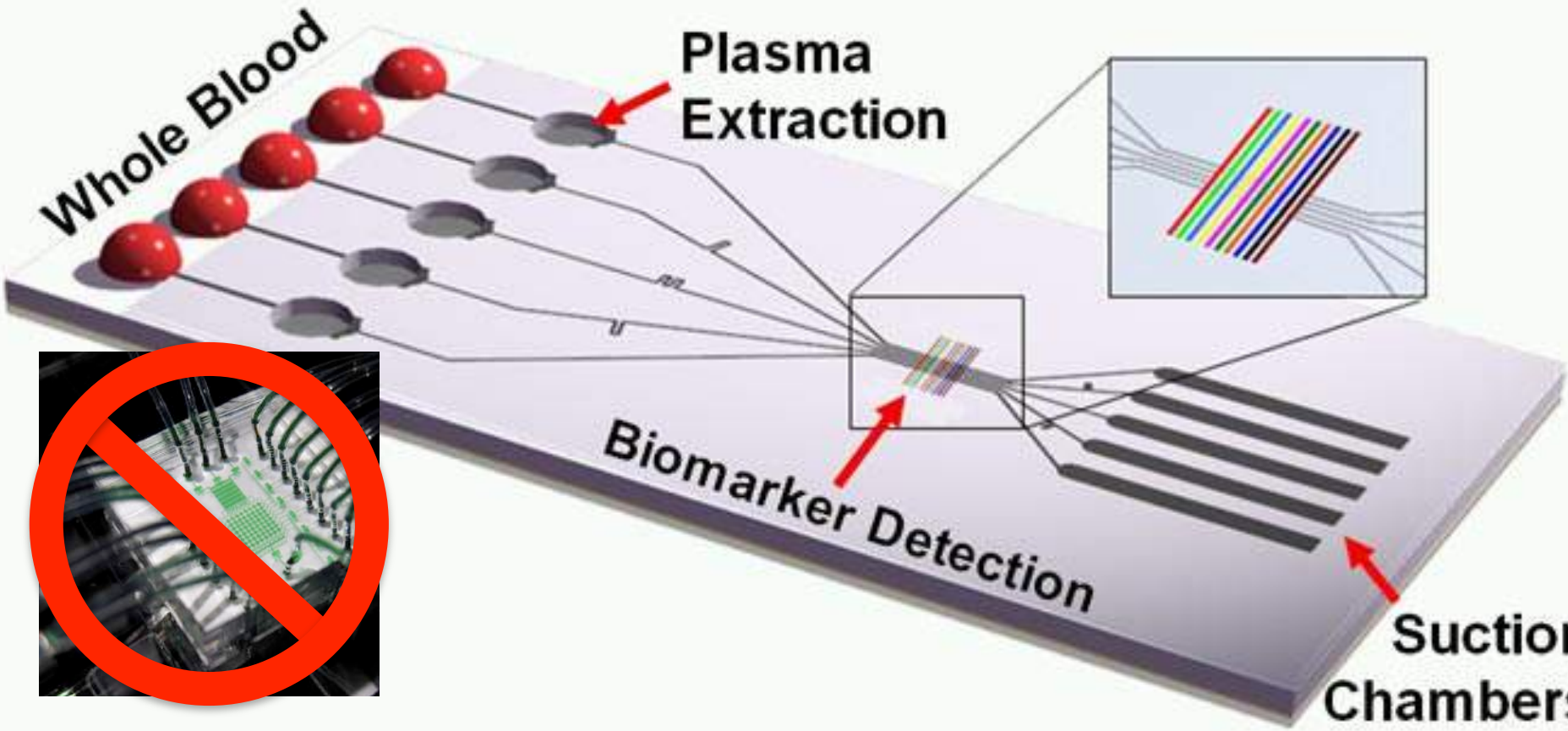
Equipment-free

Deliverable

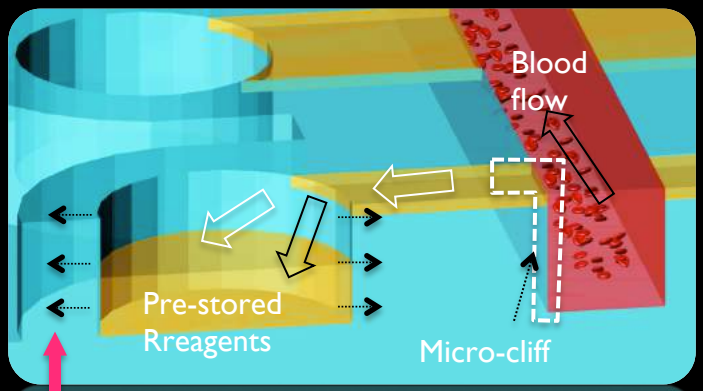




Self-powered Integrated Microfluidic Blood Analysis System (SIMBAS)

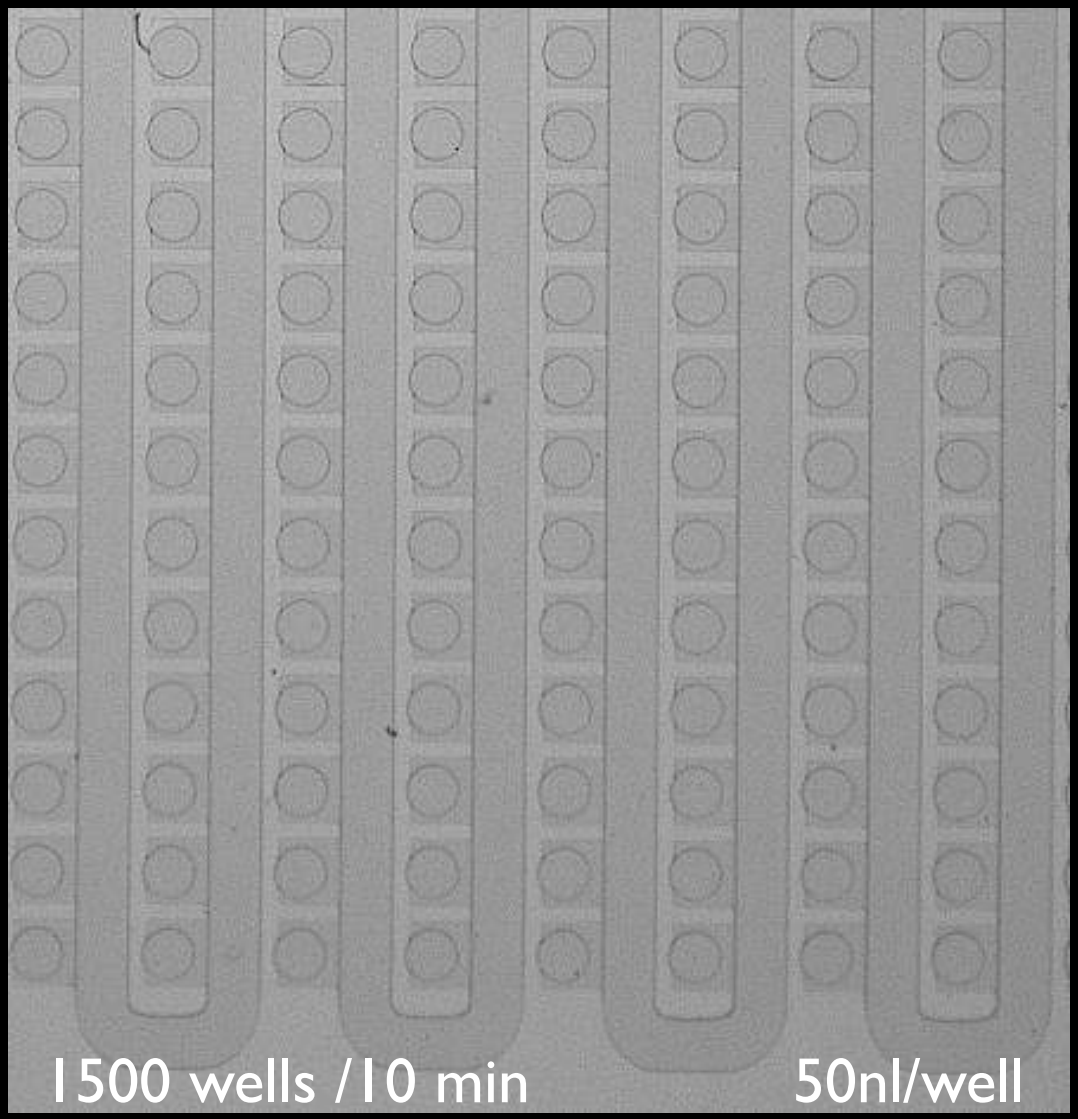


Self-digitization of *Blood Plasma*

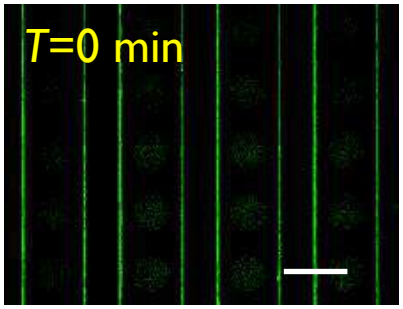


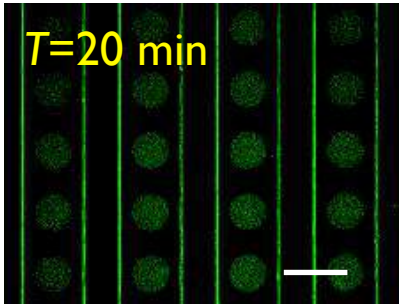
Degassing

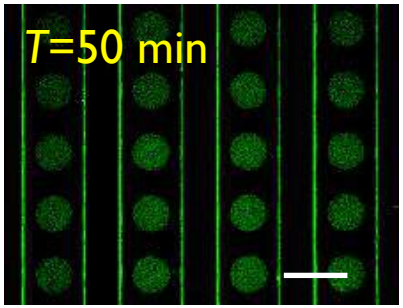
1. Blood loads by degas driven flow, RPA
2. Plasma separation enables digital-cliff structure, air plug compartmentalizes samples.
fluorescence readout.

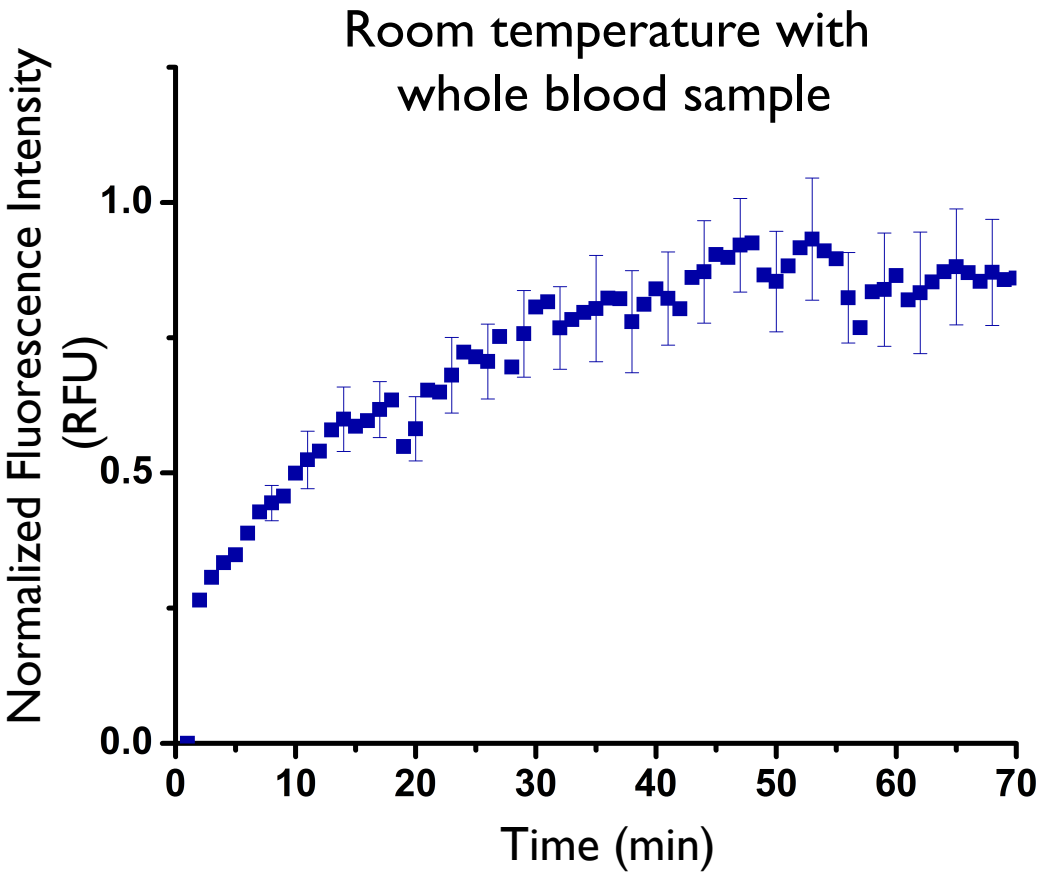


DNA Detection: On-chip RPA



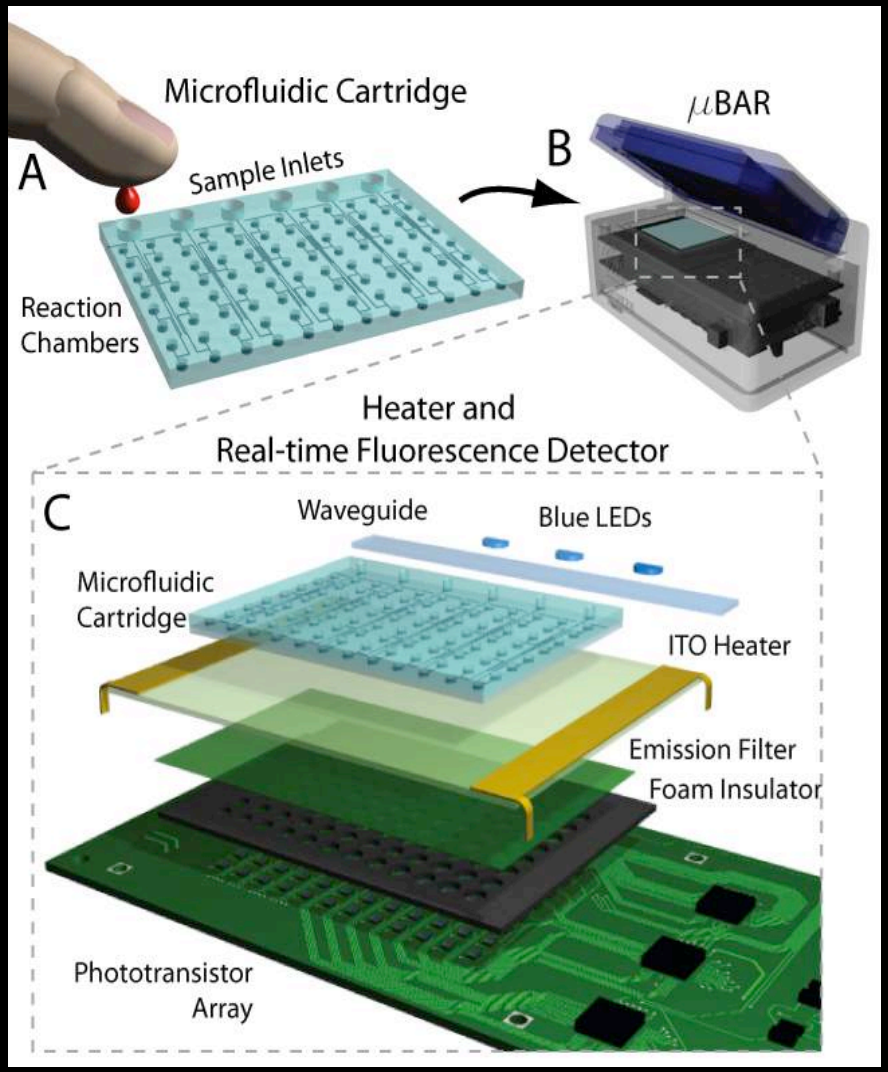






1000 copies template DNA/ μ l, 50 nl/well

Mobile Healthcare: POC Genomic Diagnostic System for Global Healthcare



- *Rapid detection & identification of ID pathogens*
- *Genomic analysis of pathogen infectivity and drug resistance*
- *Battery-powered (3.7 V)*
- *Blue LED (472 nm)*
- *Phototransistors (515 nm)*
- *Automation via microcontroller & USB interface*
- *SD Flash memory card reader*
- *GSM cell phone module*
- *GPS module*

Myers et al., PLOS ONE 2013

Patient-Specific iPSCs-based

iMAPs

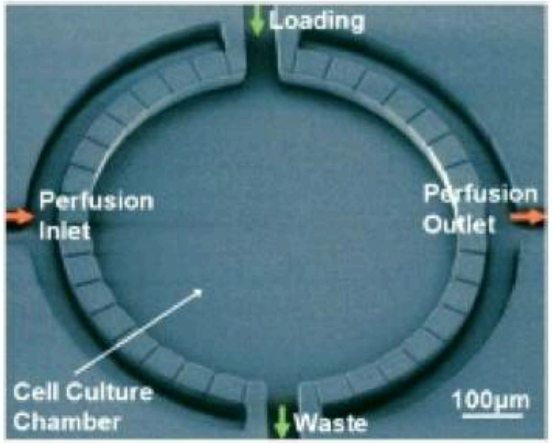
Integrative

Microphysiological

Analysis

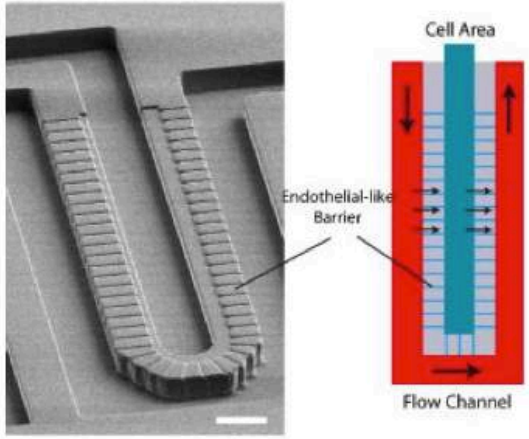
Platforms

History of Organ on Chip



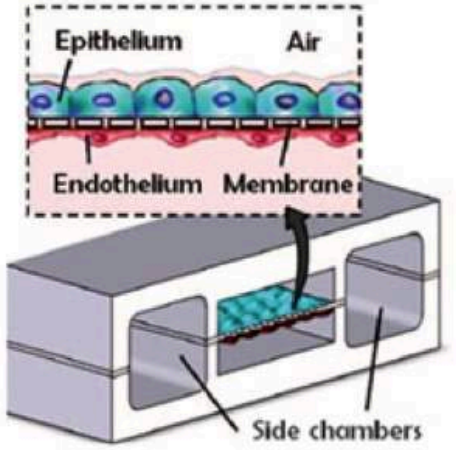
Dynamic cell culture system
(Berkeley)

2005



Liver-on-a-chip
(Berkeley)

2007



Lung-on-a-chip
(Harvard)

2010

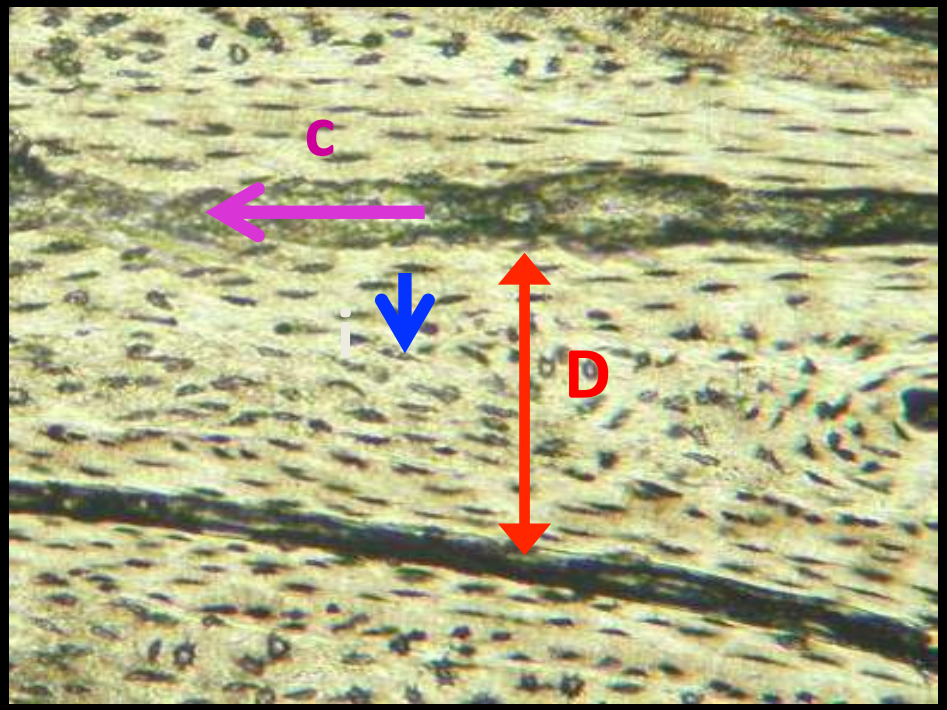
History of Cell Culture

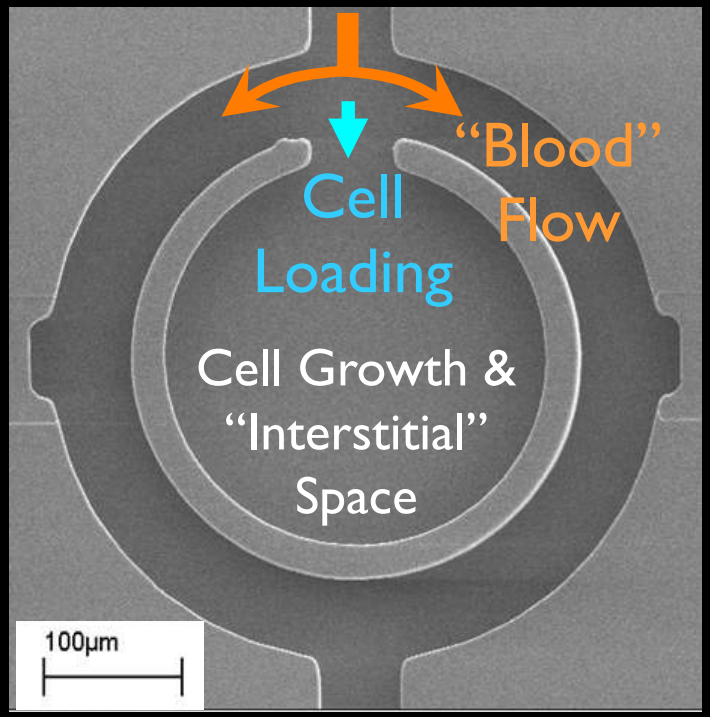
Julius Richard Petri (1852 – 1921)
German microbiologist who is credited with inventing the Petri dish while working as assistant to bacteriologist Robert Koch.

Robert Heinrich Herman Koch (1843-1910)
Considered to be the founder of modern bacteriology.
Nobel Prize in Medicine (1905)

Recapitulating Physiology:

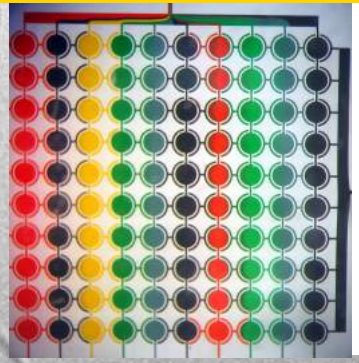
Physiologically Relevant μ-Environment

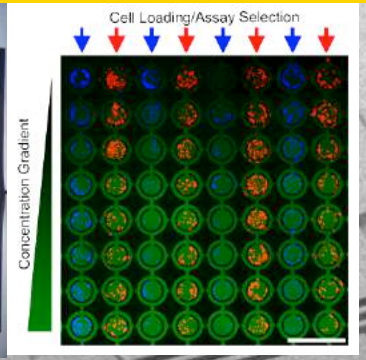


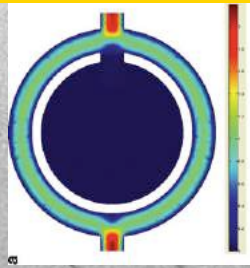


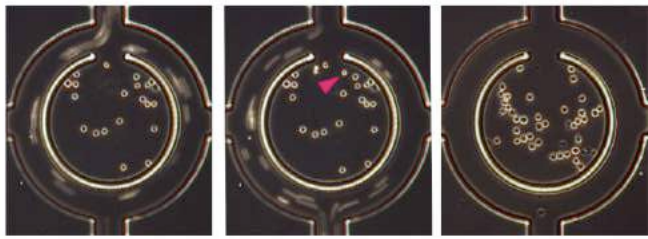
	Tissue	Microfluidic
Size (D)	100-300 μm	50-1000 μm
Circulatory Flow (c)	700 μm/s	80-4,000 μm/s
Interstitial Flow (i)	0.1 μm/s	0.08-4 μm/s
Extracellular Matrix	Complex	Surface Coating

Nanoliter Scale Microbioreactor Array for Quantitative Cell Biology

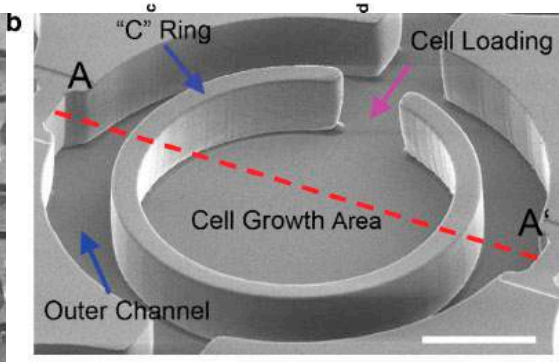


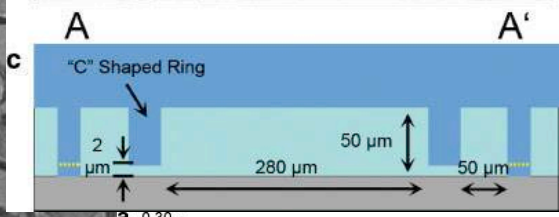


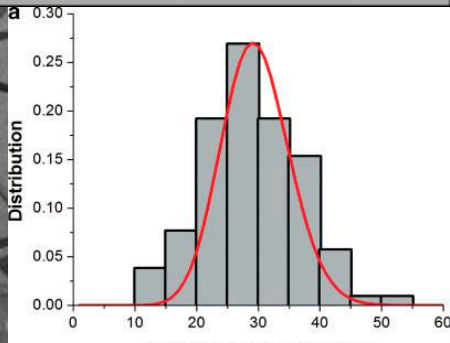




Cell Culture Array



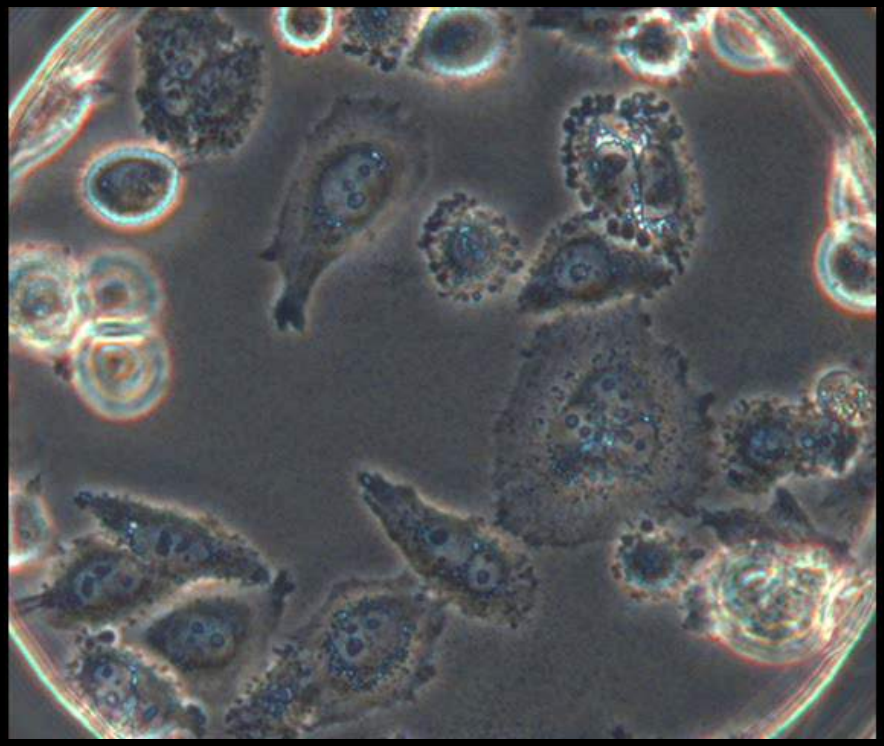




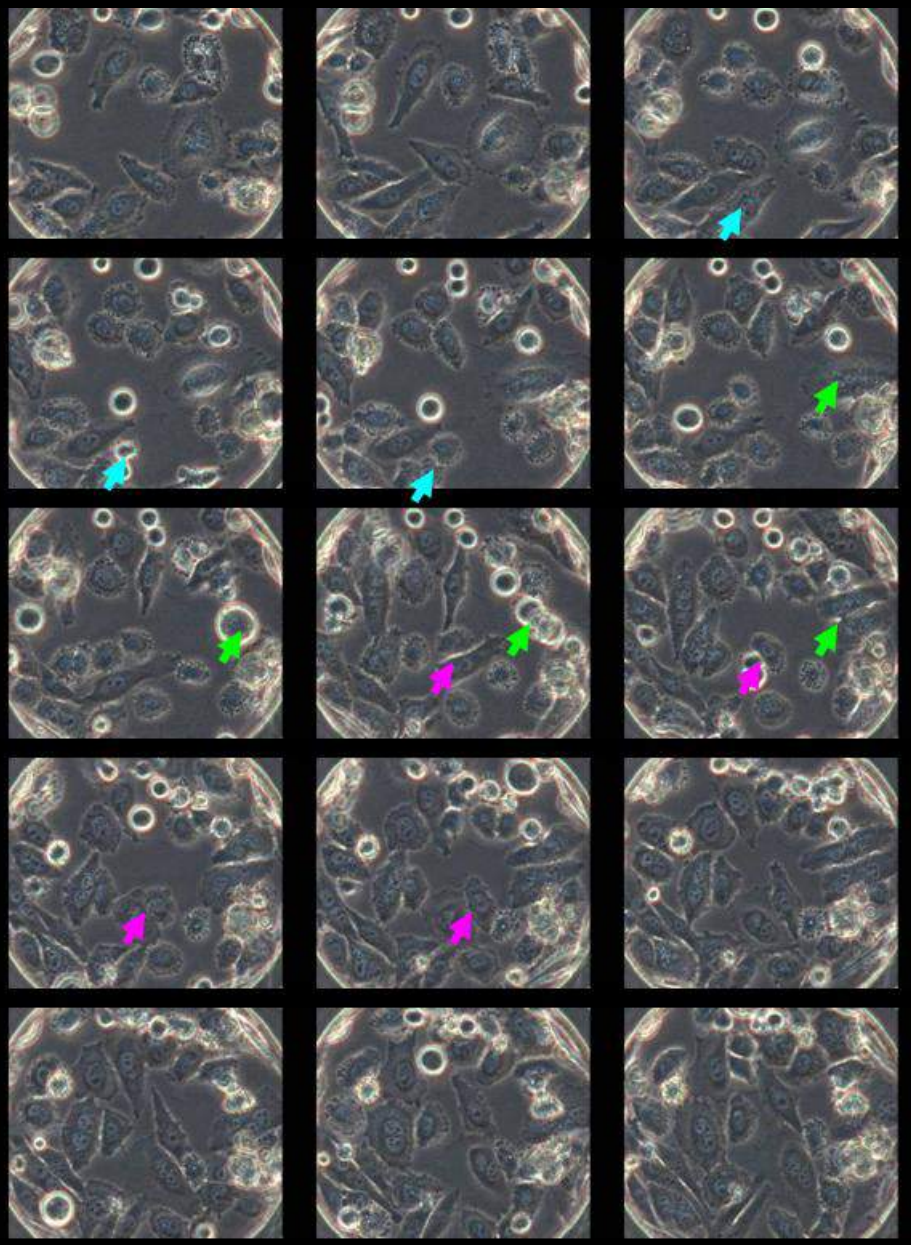
Concentration Gradient Generator

Lee et al., Biotechnology & Bioengin, 94 (1), 5-14 (2006)

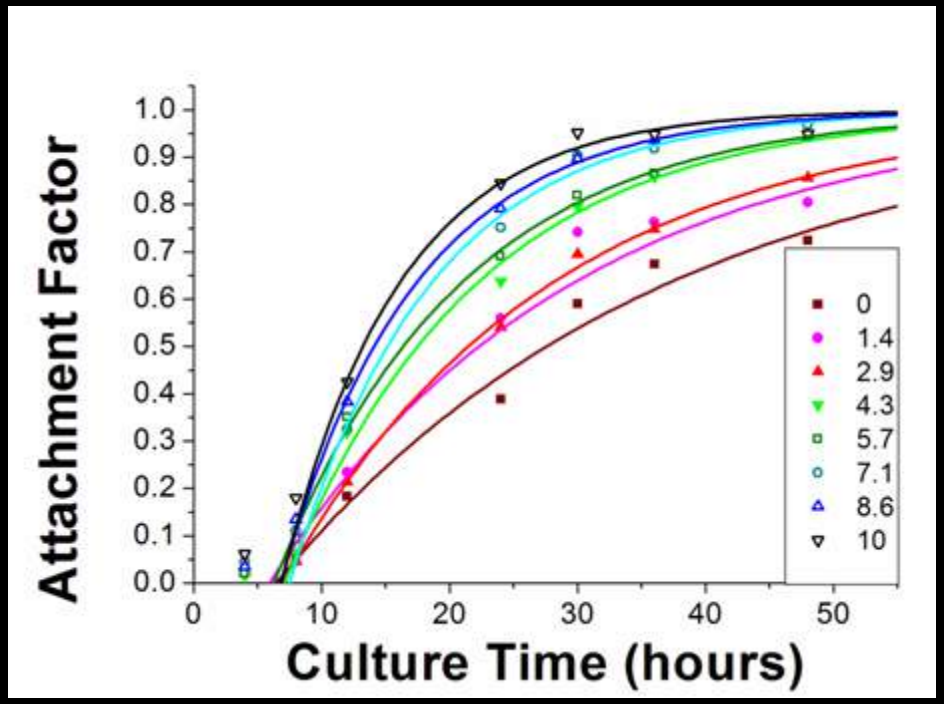
Dynamic Cell Culture Chip



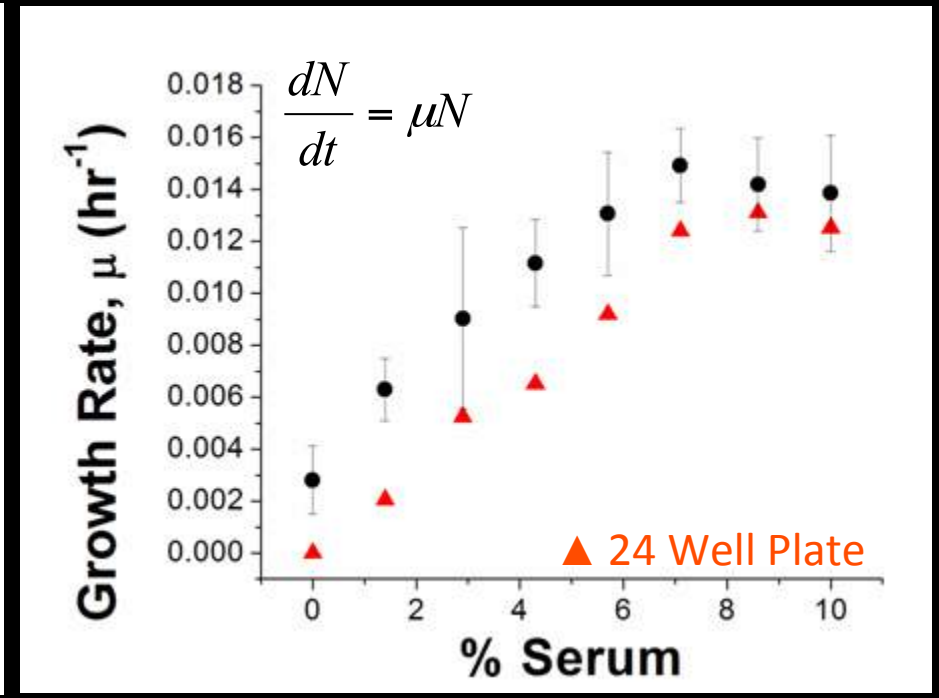
Cell Growth (HeLa, 30 min/ frame, 38 hours)



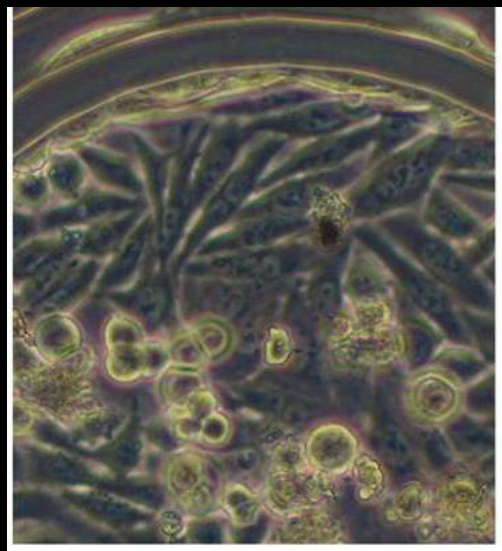
Quantitative Characterizations



Cell Attachment Kinetics

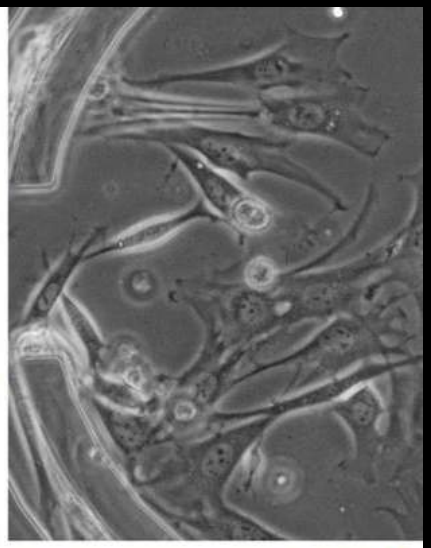


Cell Growth Rate

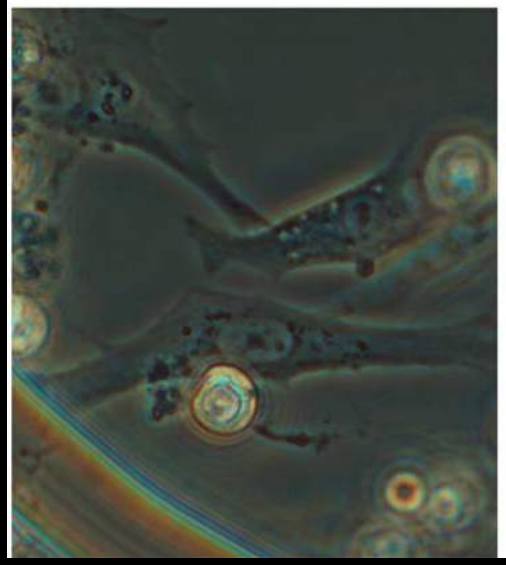


HeLa

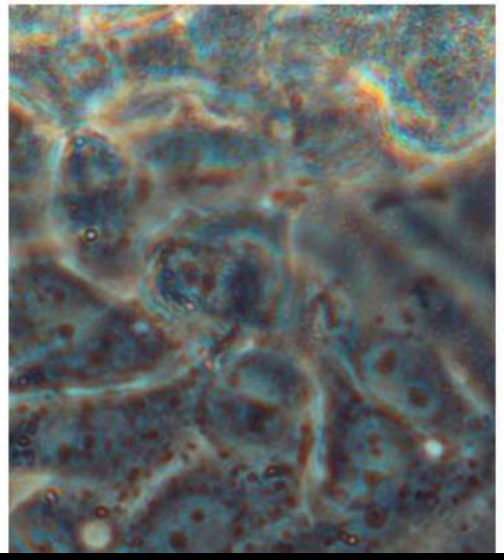
HeLa “tumor”



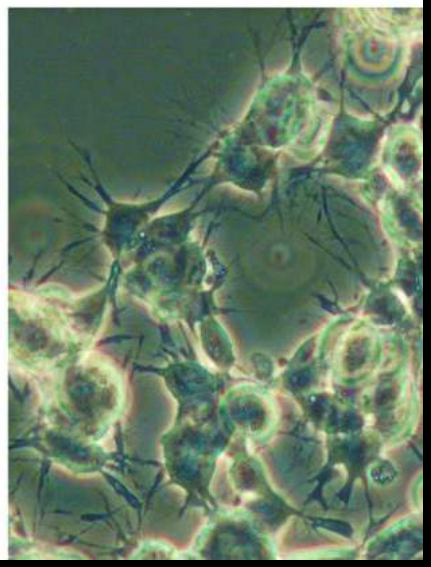
NIH3T3 Fibroblast



Primary BAEC

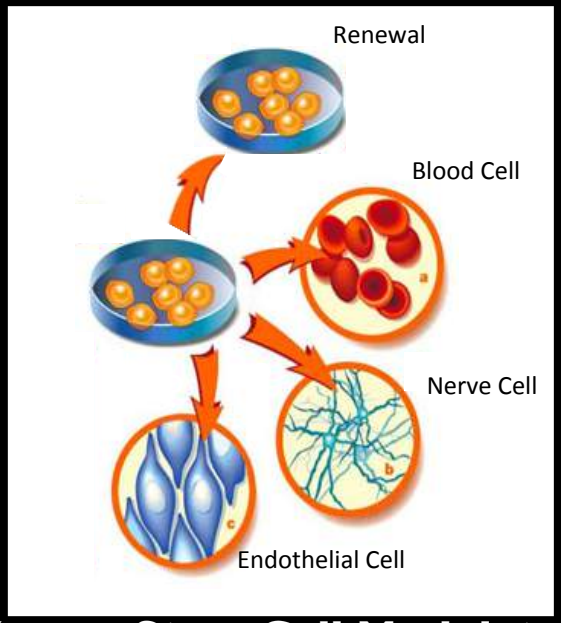


HepG2 Hepatocyte



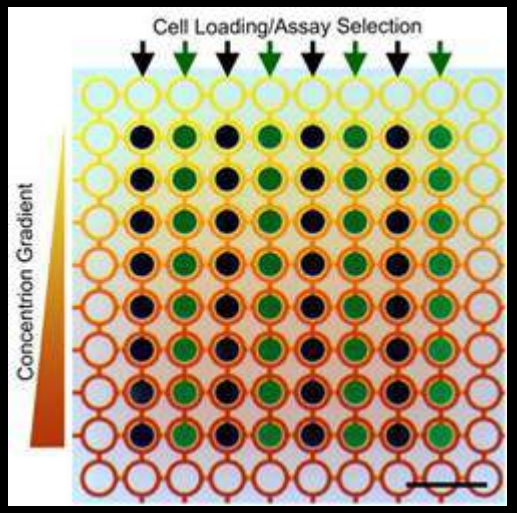
SY5Y Neuroblasts

Needs for Precision Stem Cell Biology

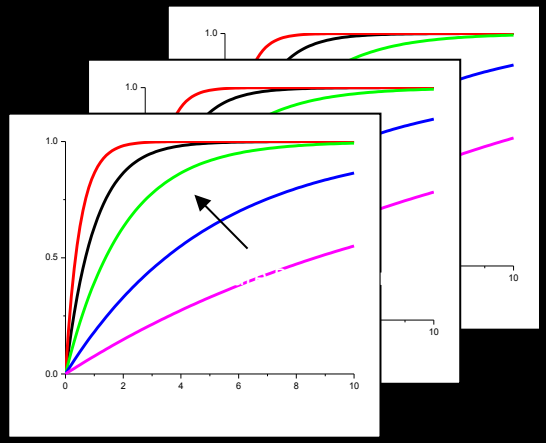


Known Stem Cell Modulators

Shear Stress
Growth Factors
Nutrient Content
ECM Contact
Surface Material
Oxygen Level
Electrical Signaling
Co-Culture
Temporal Modulation
Genetic Manipulation



Precision Biology & High Throughput Experimentation



Data Analysis and Optimization

PALS

BASIC #5

*P*hysiologically-*inspired*

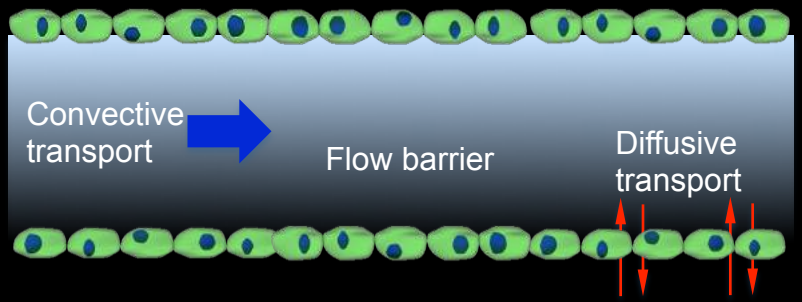
*A*rtificial

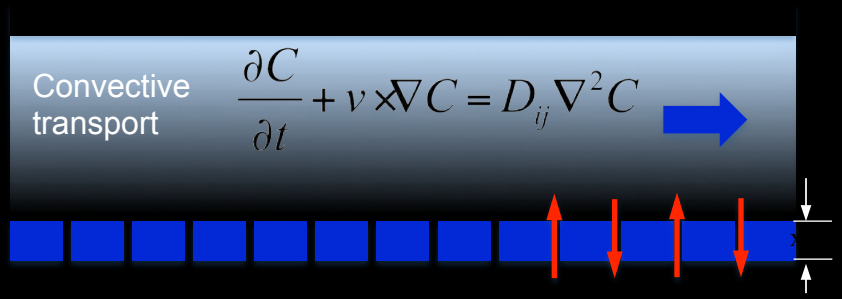
*L*iver

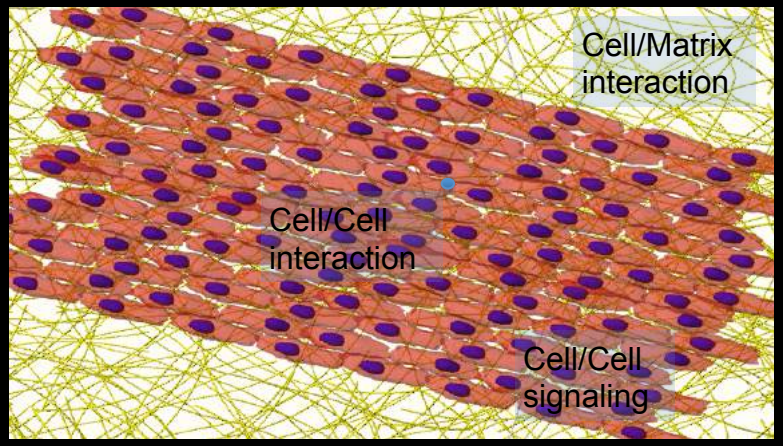
*S*inusoids

Lee & Hung *et al., Biotechnology and Bioengineering (2007)*

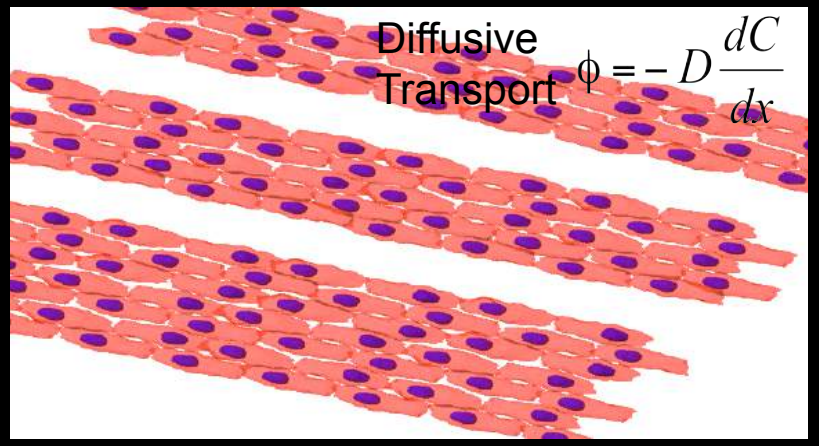
Physiologically Relevant Dynamic Cell Culture for Precision Medicine







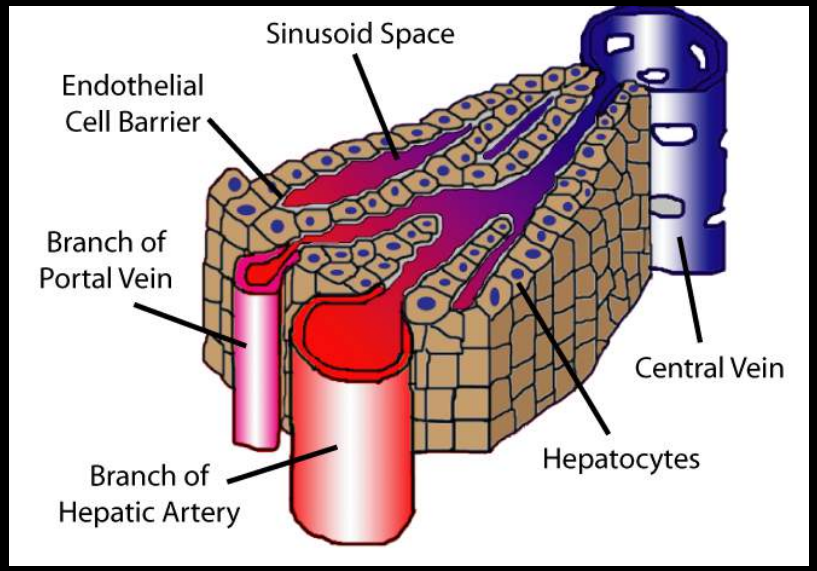
In vivo

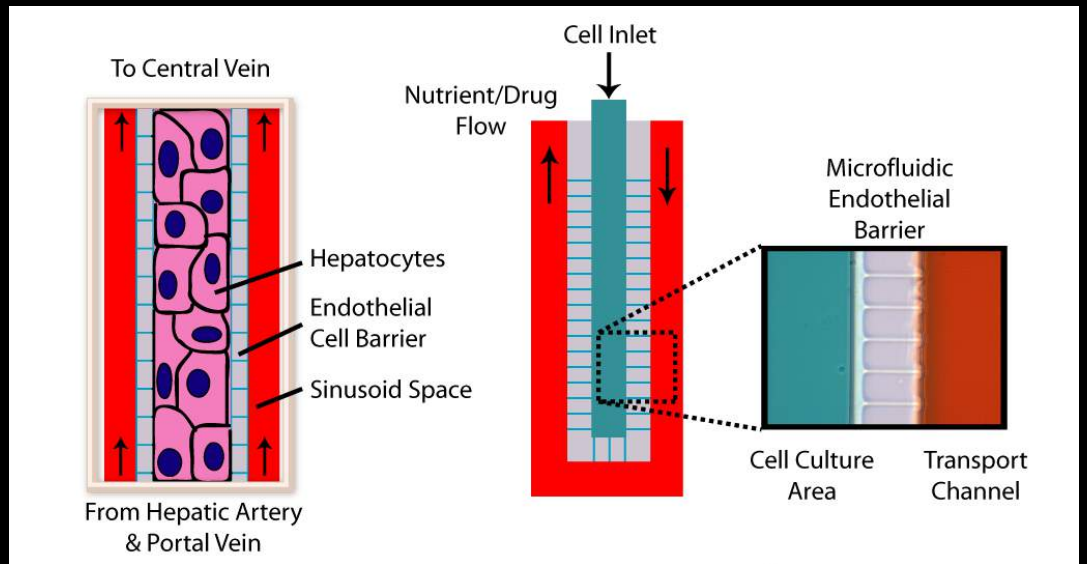


Cultured Cells

1. Understand physiologically relevant microenvironments
2. Use precision microengineering to create better cell environments
3. Precision biological perturbations, real time and continuous monitoring

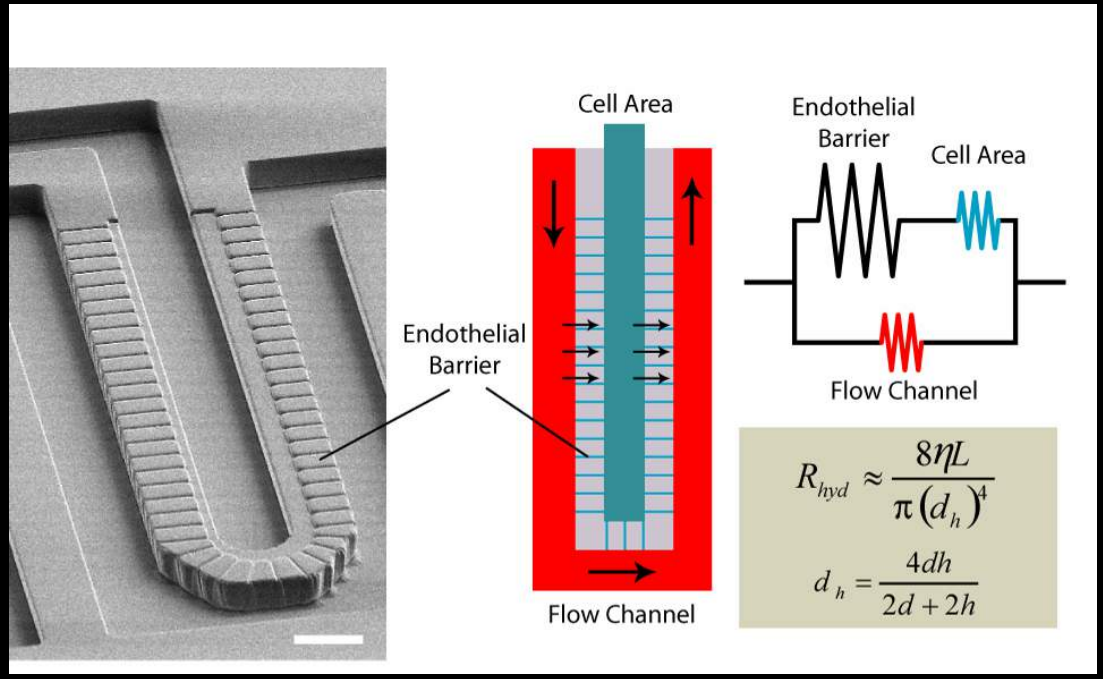
Physiologically-inspired Liver Architecture on Chip





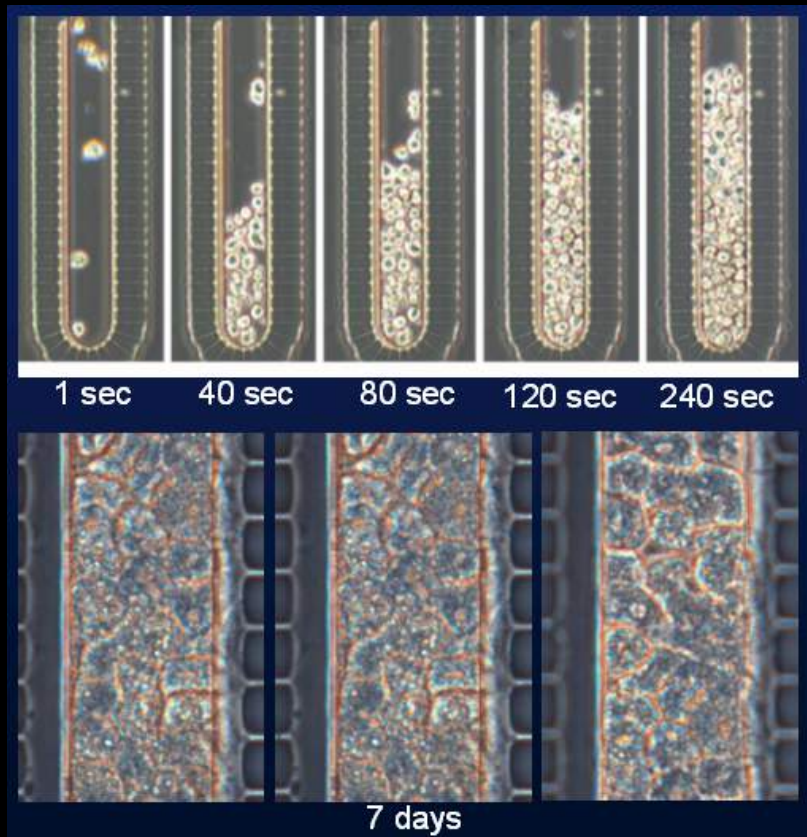
- Sinusoid space transports blood to hepatocytes
- Lined with fenestrated endothelial barrier
- Hepatocytes form extensive cell-cell contact

Physiologically-inspired Artificial Liver Sinusoid

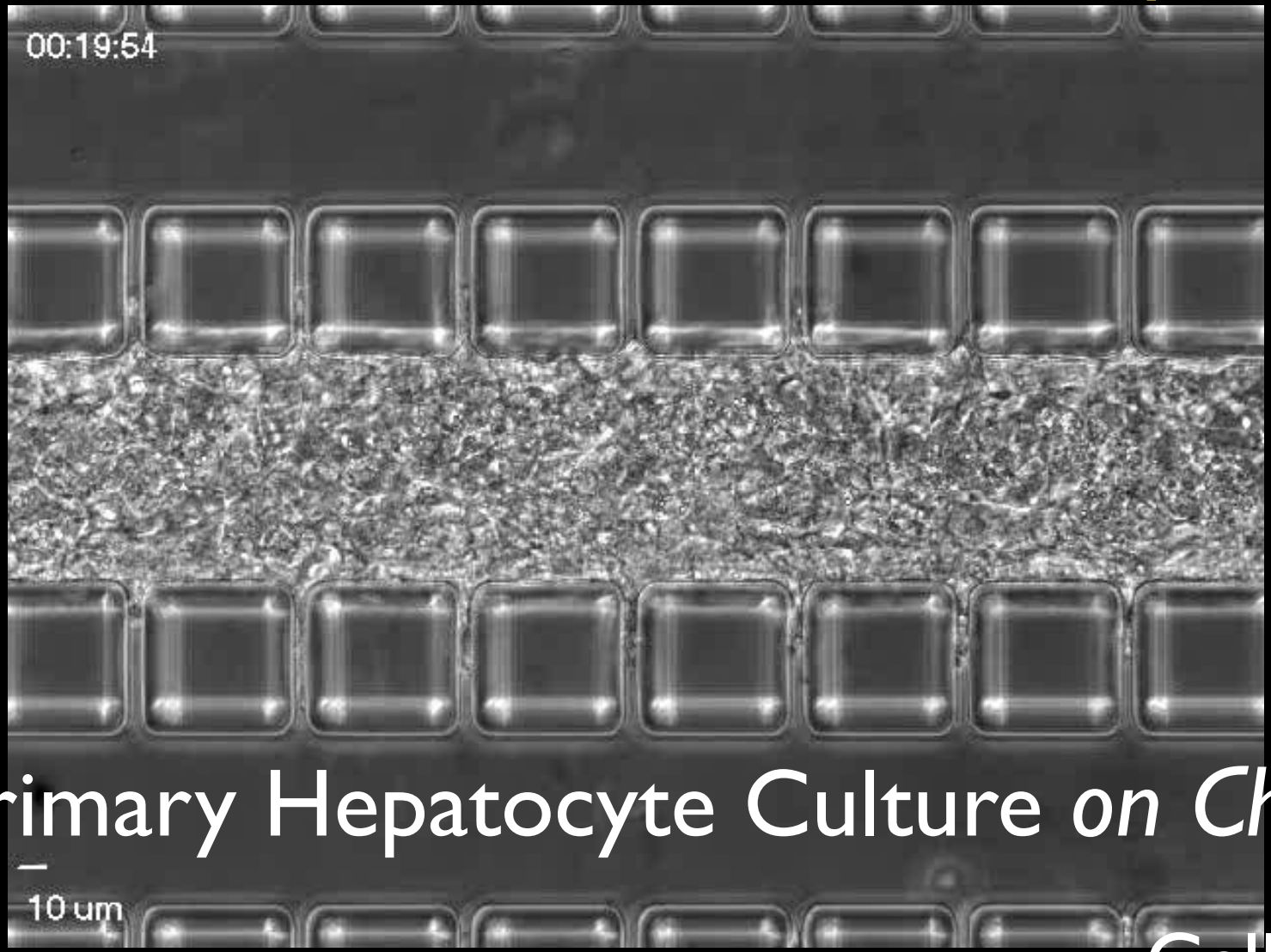


- Microfluidic endothelial barrier
- High density hepatocyte culture
- Continuous flow mass transport

Precision Control of Hepatocyte Loading



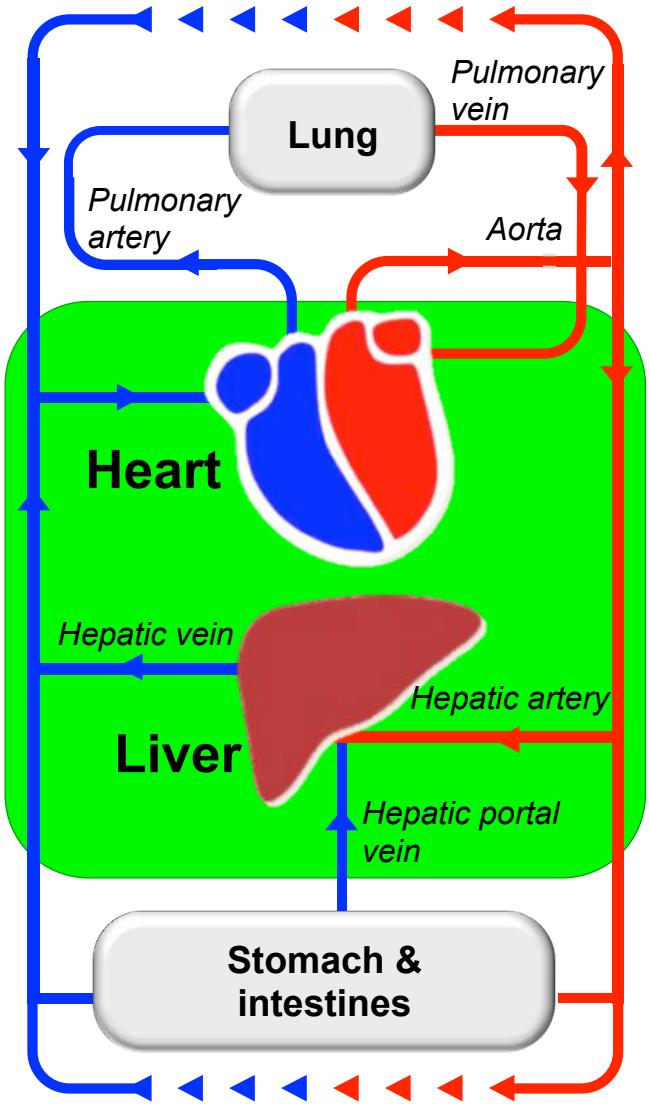
Physiologically-inspired Liver Architecture on Chip



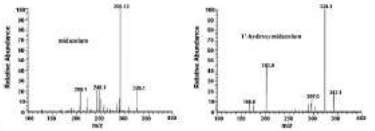
Primary Hepatocyte Culture *on Chip*

CellASIC

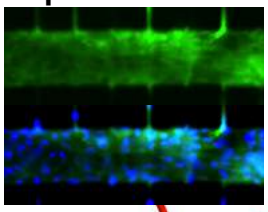
Patient-Specific iPSCs-based Integrative Microphysiological Analysis Platforms (iMAPs)



Mass Spectrometry



Optical Microscopy

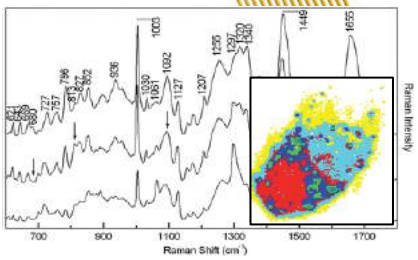


hiPS-CMs on Chip

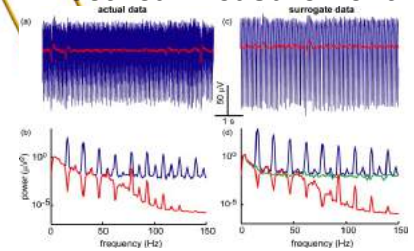
hiPS-HPs on Chip

Real Time Sampling

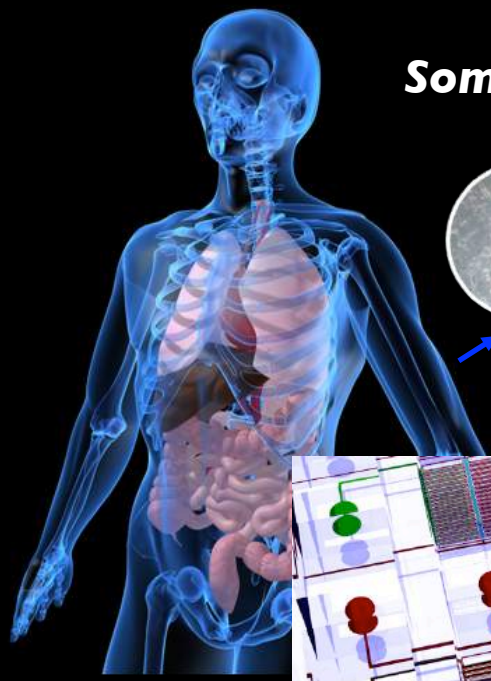
Raman Microscopy



Electrical Measurement



iMAPs for Personalized Medicine

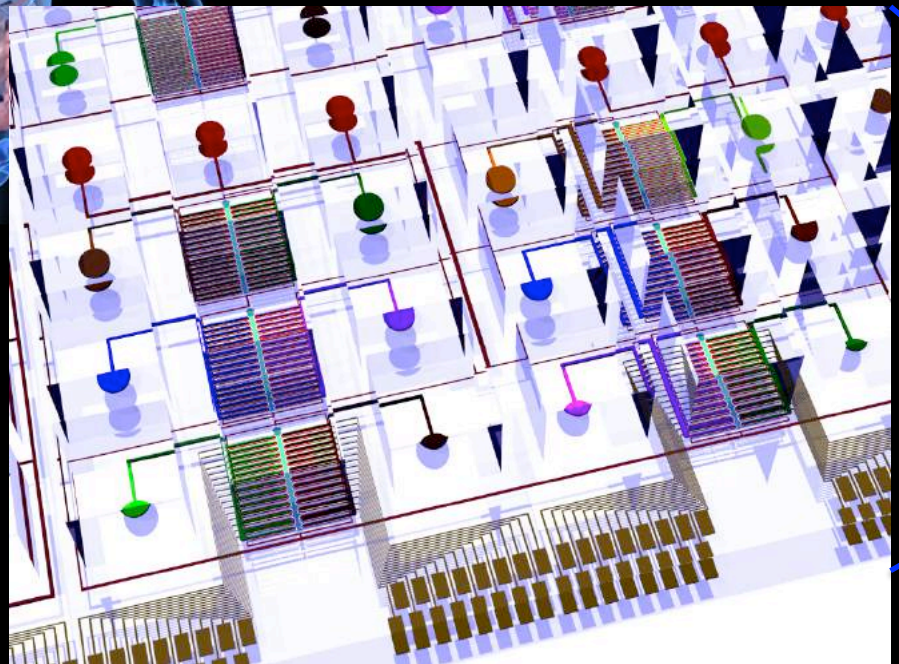


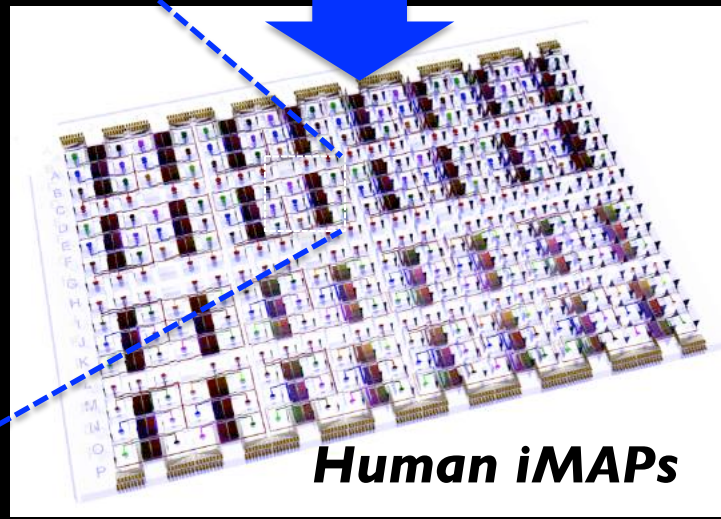
Somatic cell

Patient-iPSCs

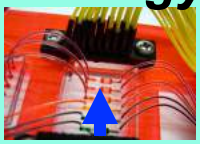
Re programming

Differentiation

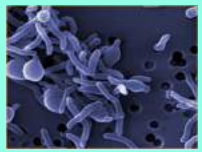


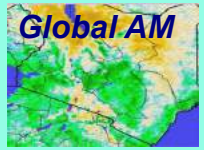


Quantitative Biology

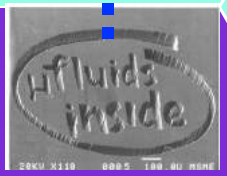


Medical Innovations

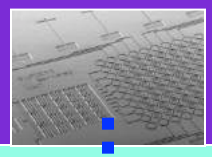




Agricultural Monitoring



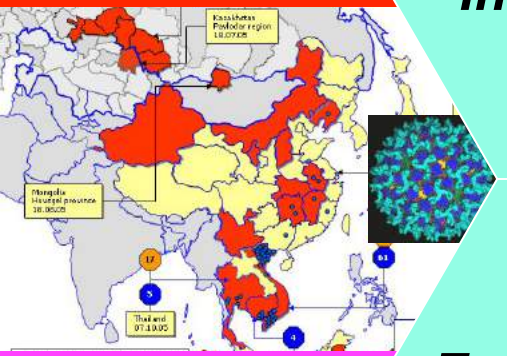
Ubiquitous iMDx & iMAPs

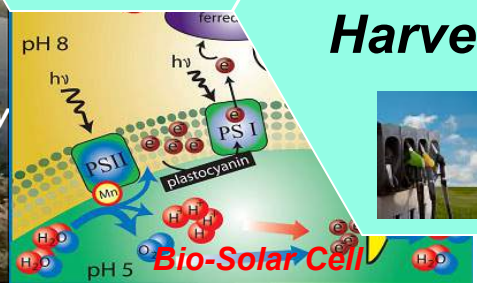


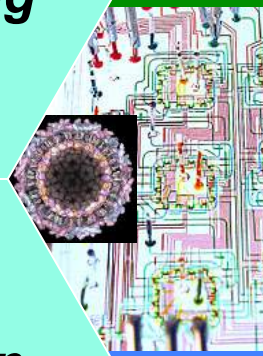
Energy Harvesting

Environmental Monitoring

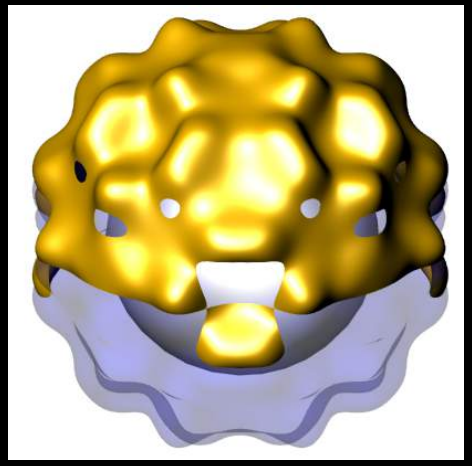
Organs on Chip for DRx







Nanoscale Additive Precision Manufacturing for Nano-Satellites

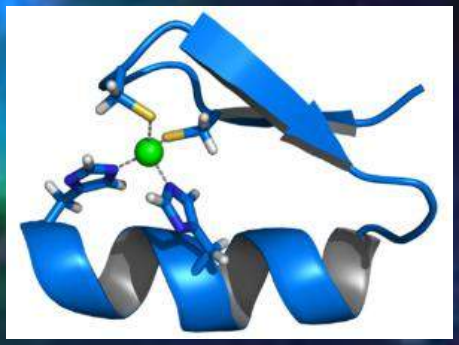


Exploring the Living Cells: Cellular Galaxy

Can We Capture *e-motions* in Living Cells?

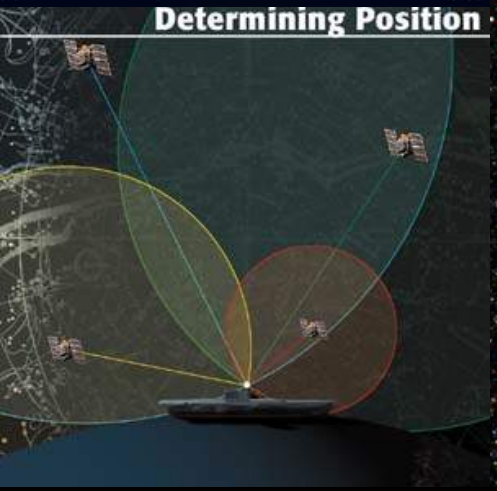
Need for Satellite Nanoscopes

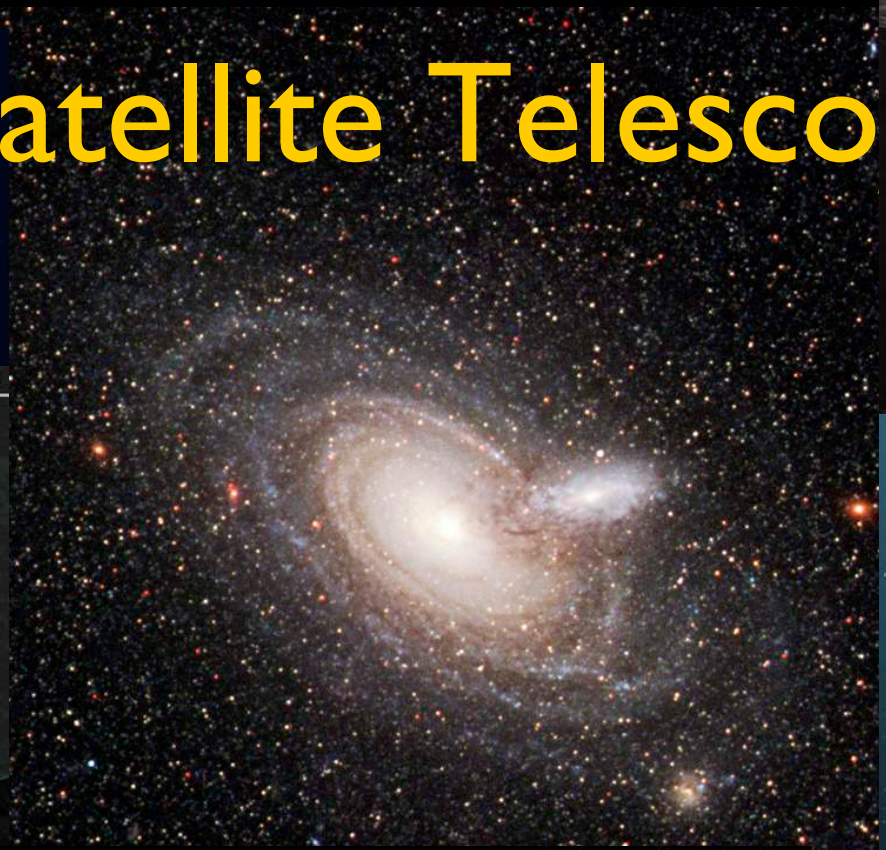
Read out e-motions:
Electronic states
Vibration states

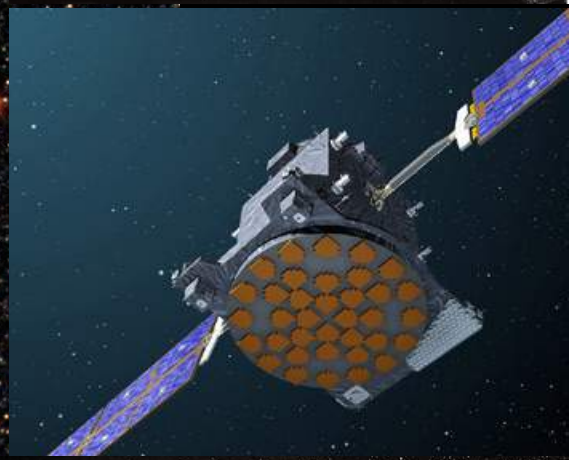


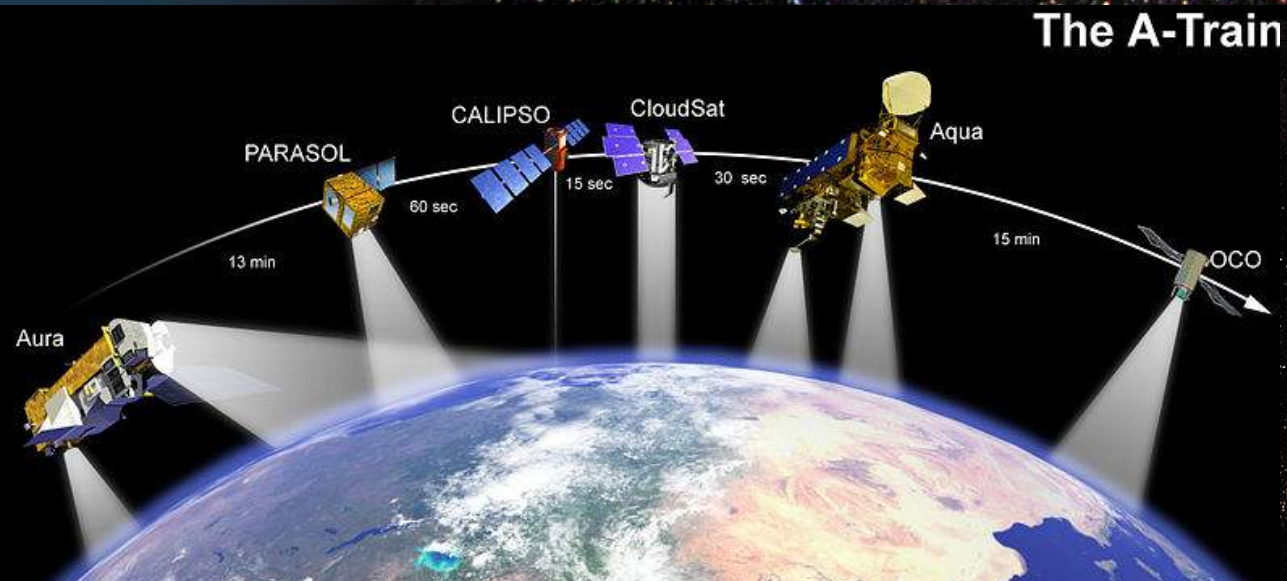
- *Monitoring & Regulating Cellular Signaling Pathways*
- *Understanding Electron Transfer Mechanism in Living State*
- *Observation of In Vivo Electron-Transport Dynamics*

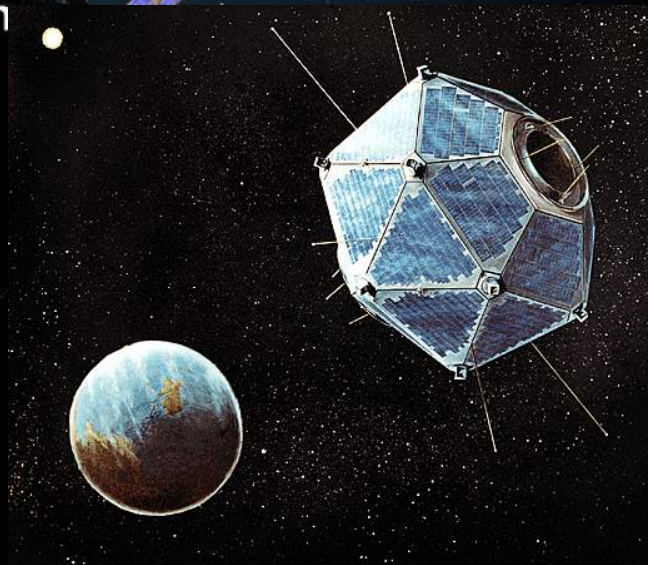
Satellite Telescopes





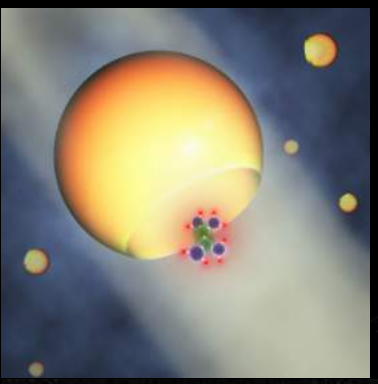


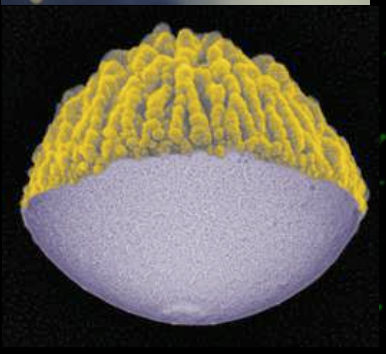




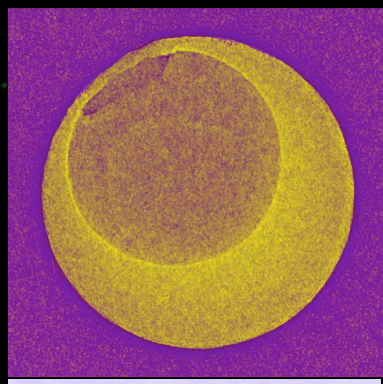
Nanoscale Satellite

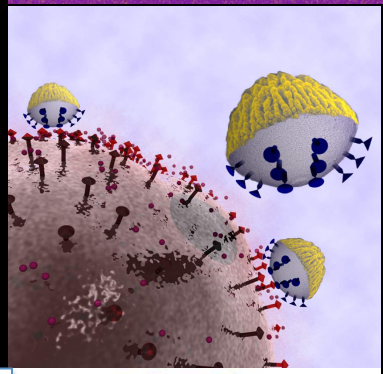
Capturing electron transfer dynamics and molecular imaging in living cells

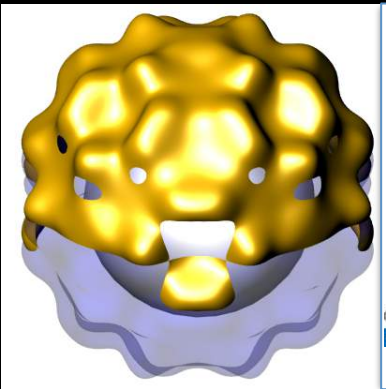


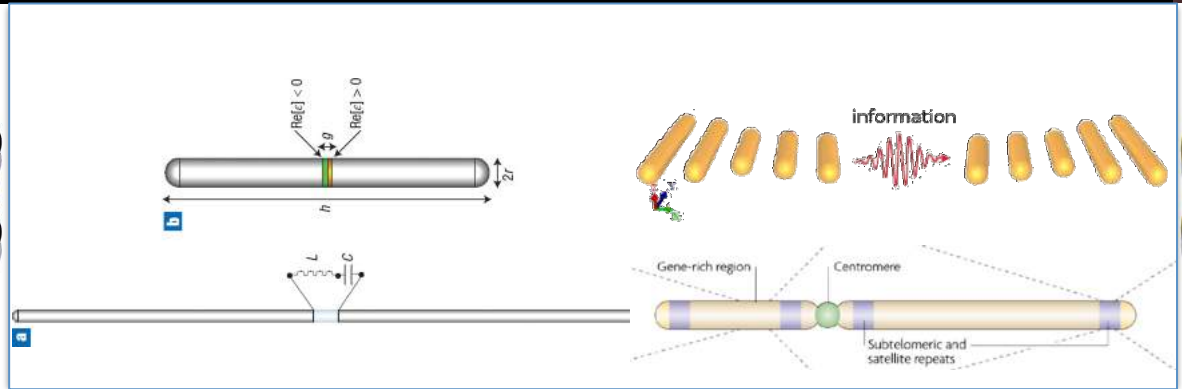


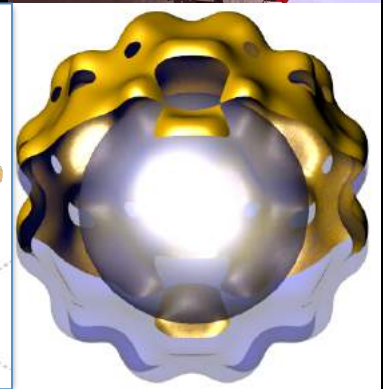
Quantum Nanoscope





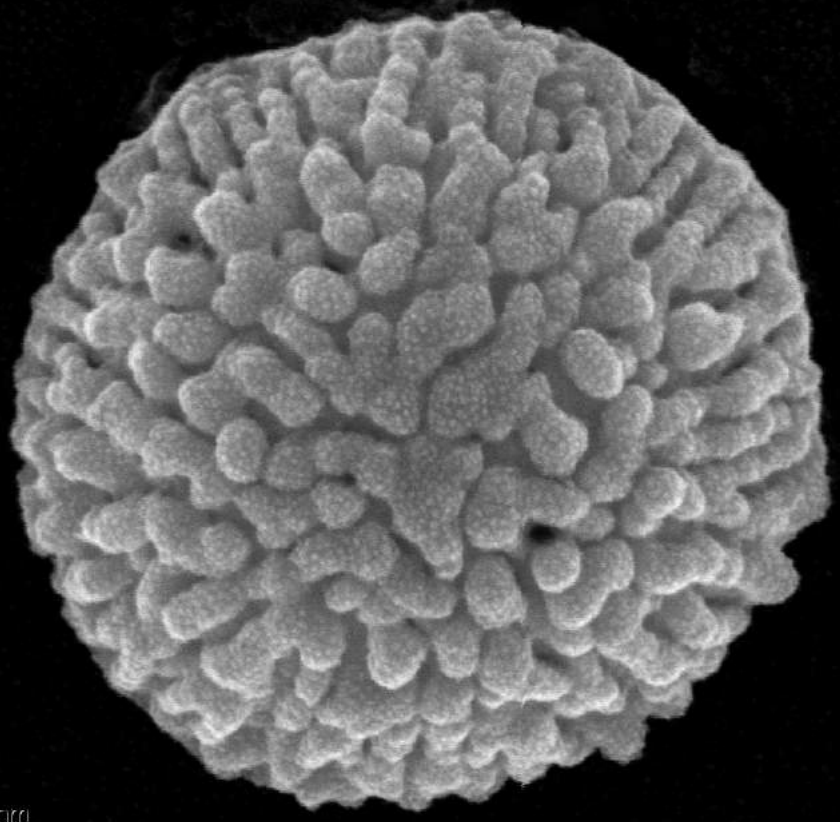


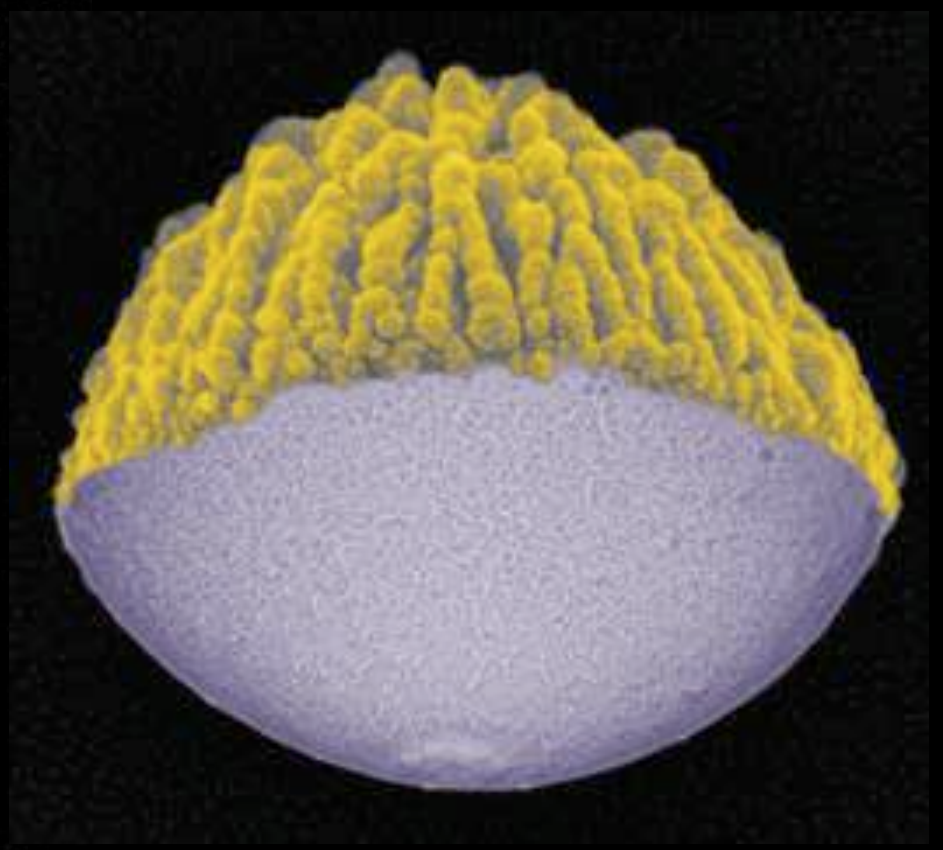




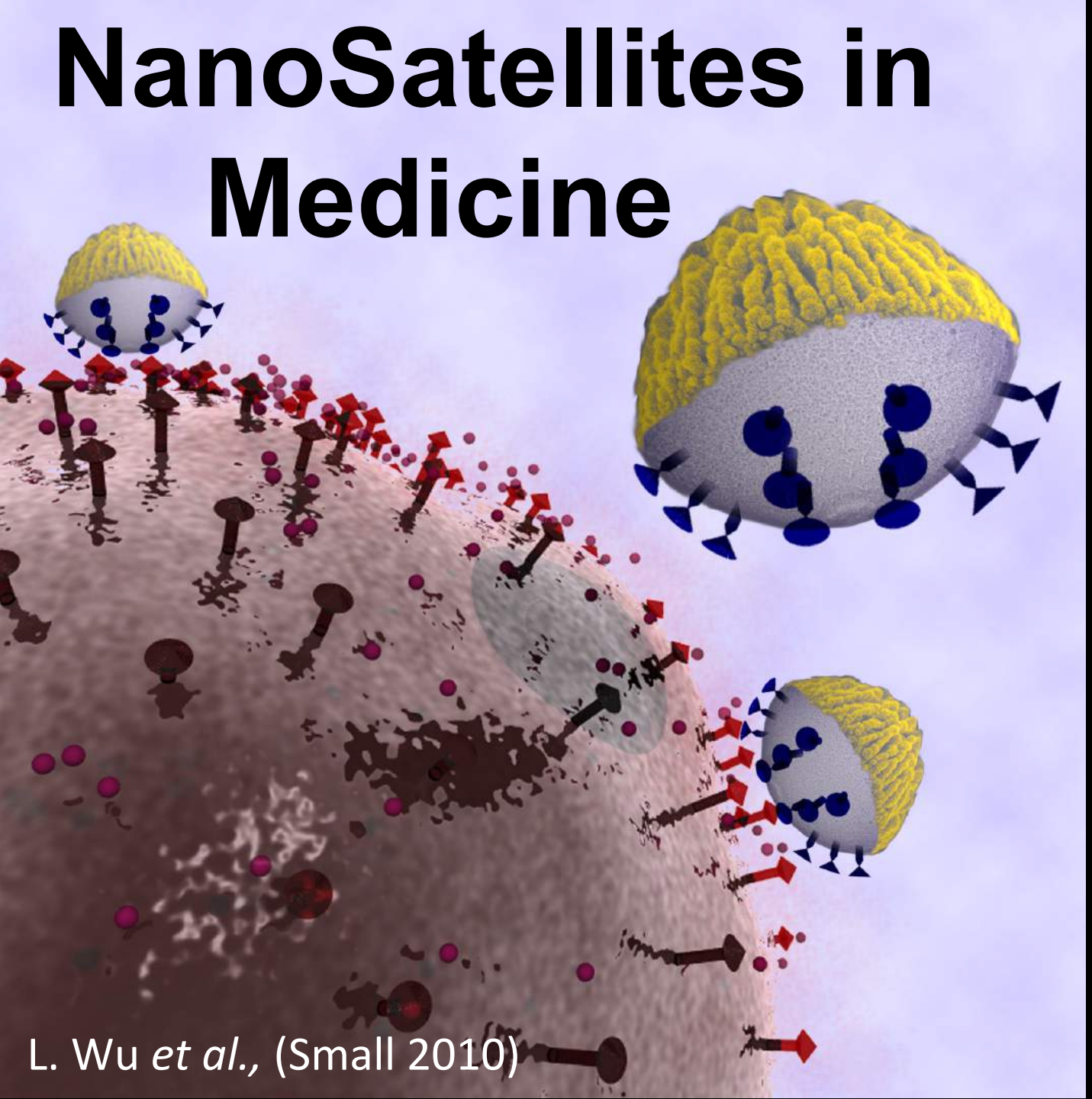
Bioinspired Nanocoral

with Decoupled Cellular Targeting and Sensing Functionality





NanoSatellites in Medicine



L. Wu *et al.*, (Small 2010)

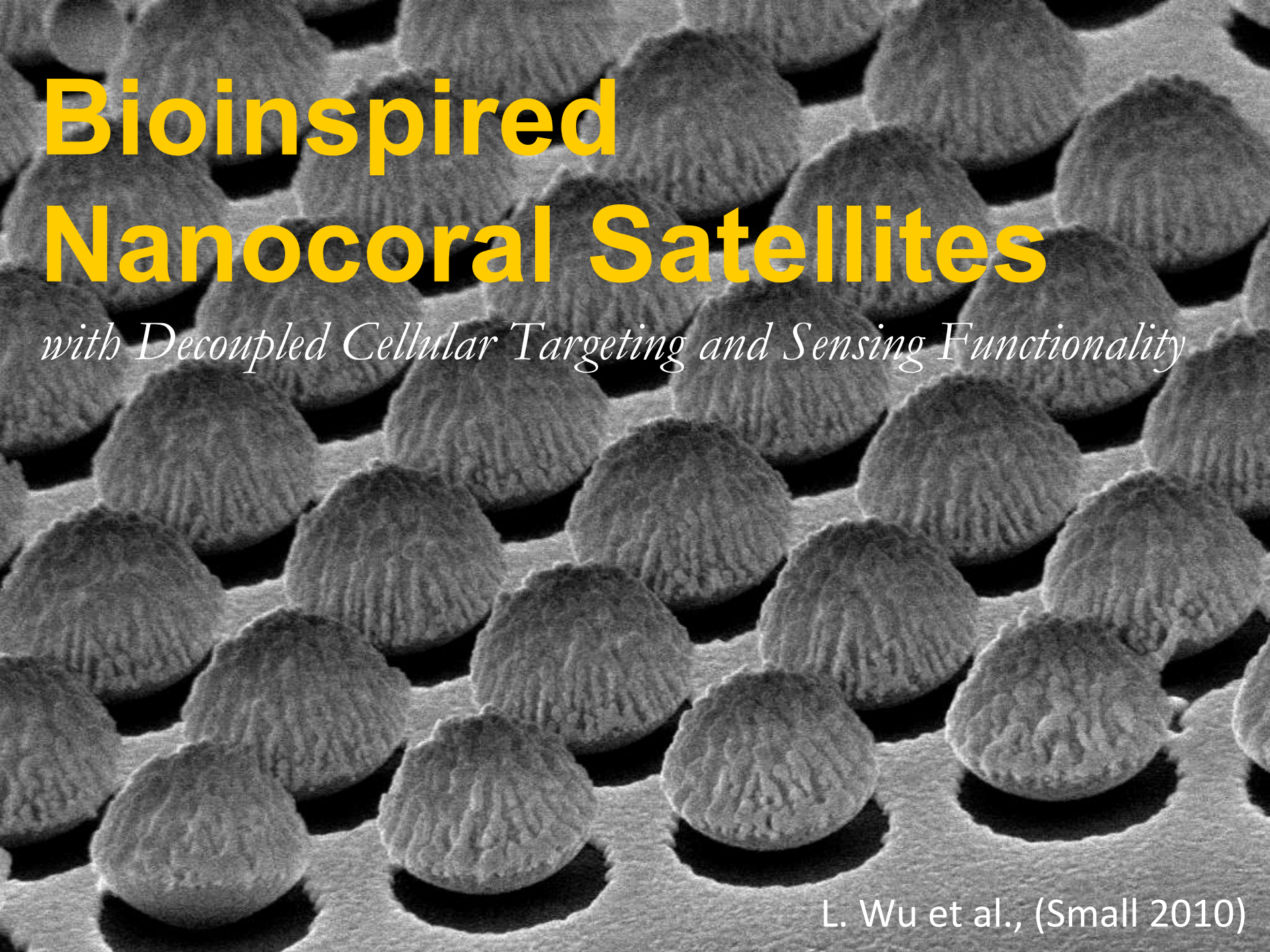
Targeting

Sensing

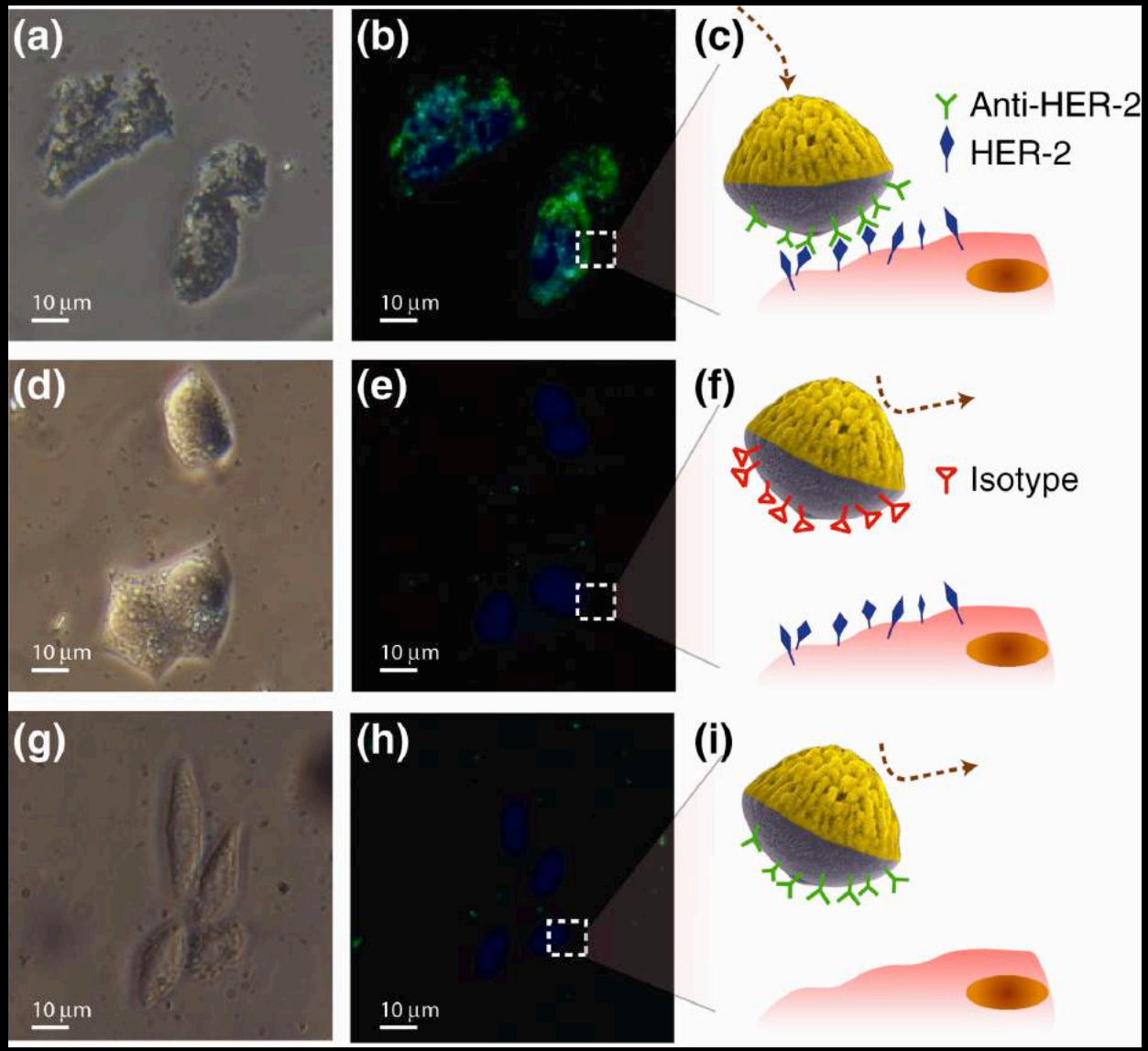
Gene Delivery

Gene Regulation

Drug Delivery


Bioinspired
Nanocoral Satellites
with Decoupled Cellular Targeting and Sensing Functionality
L. Wu et al., (Small 2010)

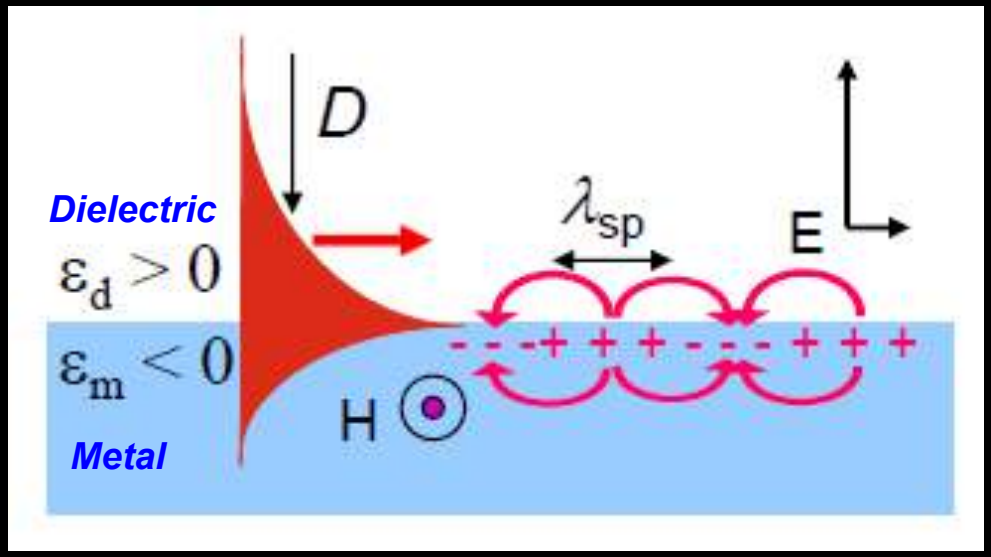
Bioinspired NanoSatellites



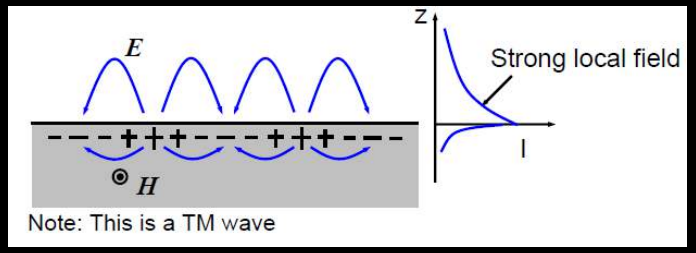
Specific Targeting Cancer Cells

Surface Plasmon Polariton

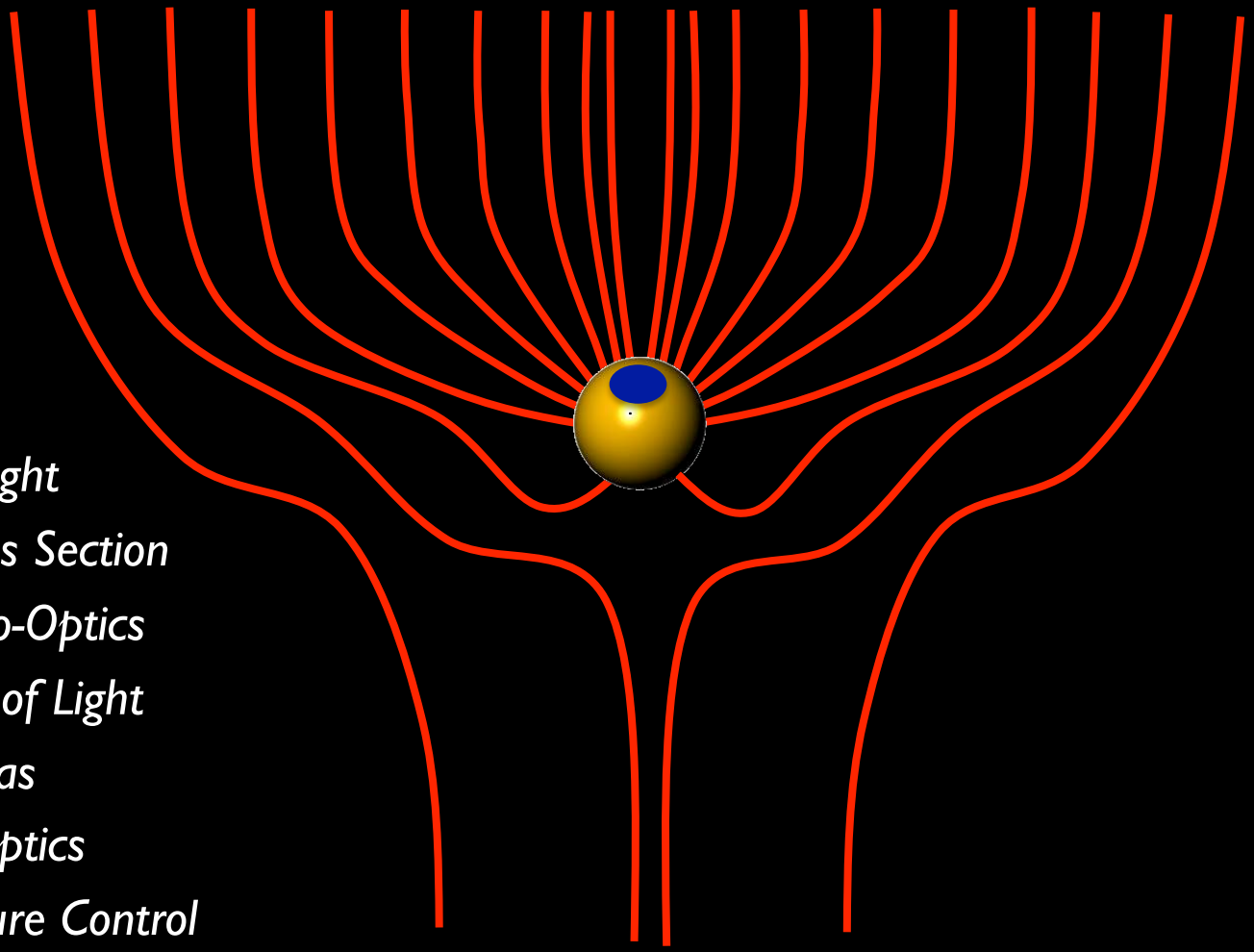
- Longitudinal coherent charge oscillation localized to a metal/dielectric boundary.
- Surface plasmon associated with evanescent electromagnetic mode.



$$k_{sp} = \frac{\omega}{c}\sqrt{\frac{\epsilon_m \epsilon_d}{\epsilon_m + \epsilon_d}}$$



Nanoplasmonic Optics

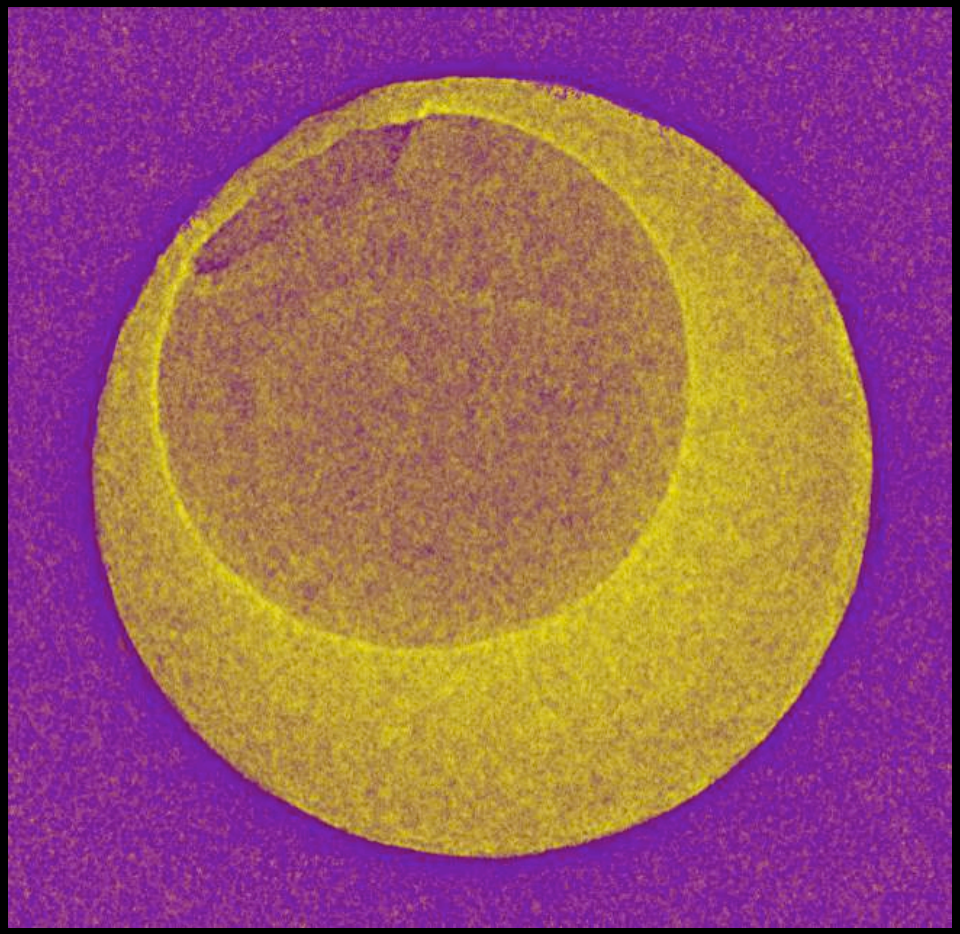


Advantages:

- *Nano-focusing of Light*
- *Strong Optical Cross Section*
- *Metamaterial Nano-Optics*
- *Directional Control of Light*
  - *Optical antennas*
- *Transformational Optics*
- *Precision Temperature Control*

Nanocrescents: *NanoSatellites*

Fiat Lux!



Y. Lu et al., (Nano Letters 2005)

Exploring Living Cellular Galaxy

by Nanoscale Satellites *with Optical Antennas, Nanoscopes, & Wireless Communication*

External Optical Signals

785 nm

1550 nm

660 nm

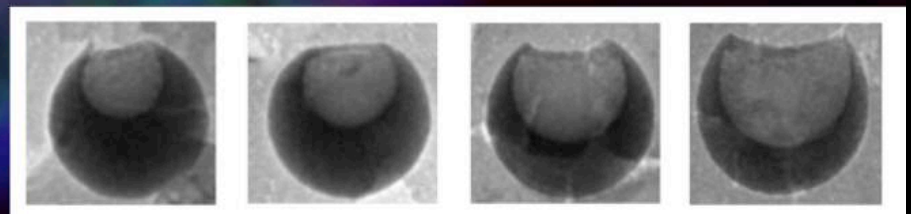
980 nm

Convergence of

- Cell Biology
- Chemistry
- Quantum Mechanics
- Molecular Engineering
- Nanotechnology

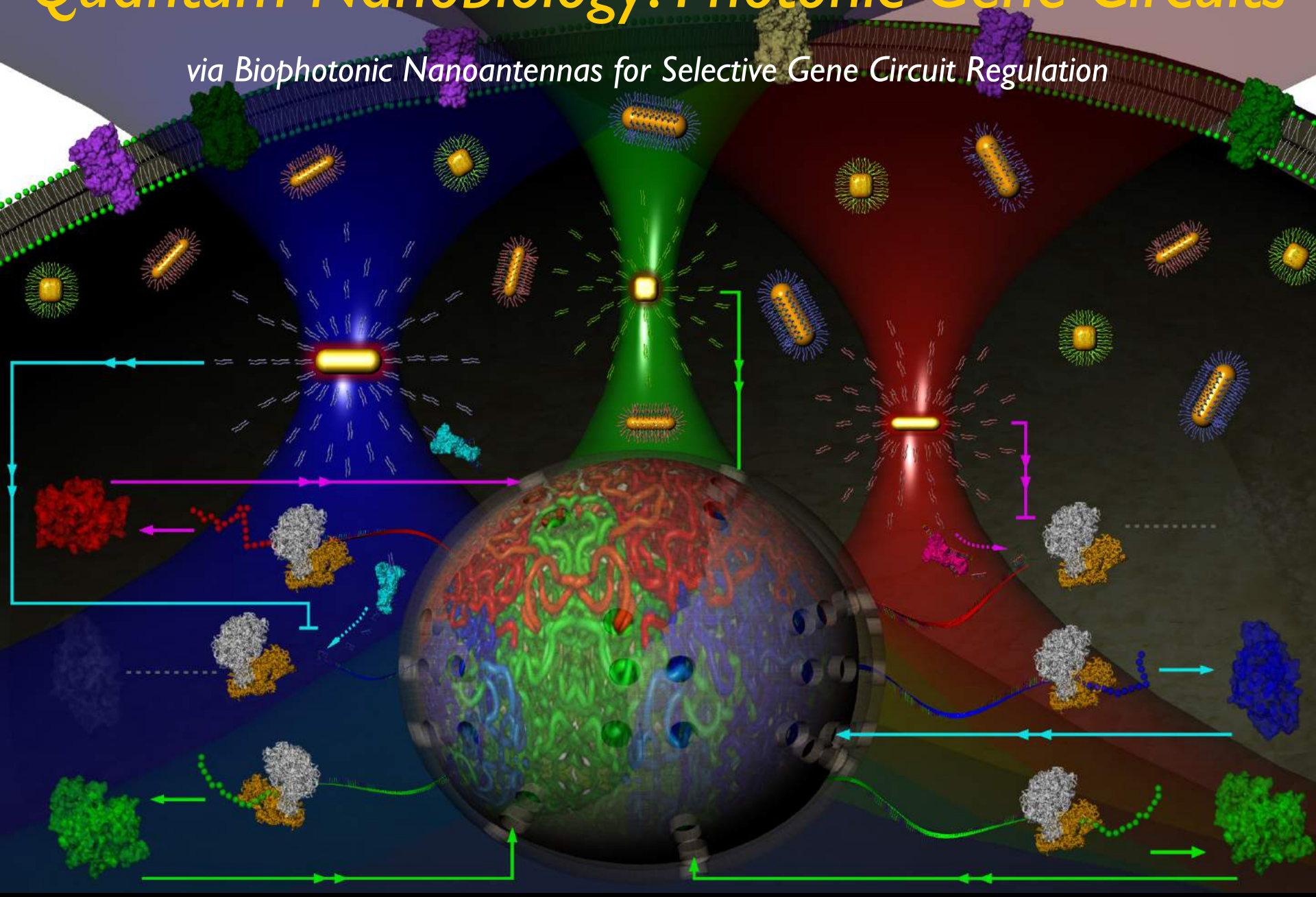
Molecular Spectroscopic Imaging of Electronic & Vibration States

"Cell" Phone Optical Antennas



Quantum Nanobiology: Photonic Gene Circuits

via Biophotonic Nanoantennas for Selective Gene Circuit Regulation

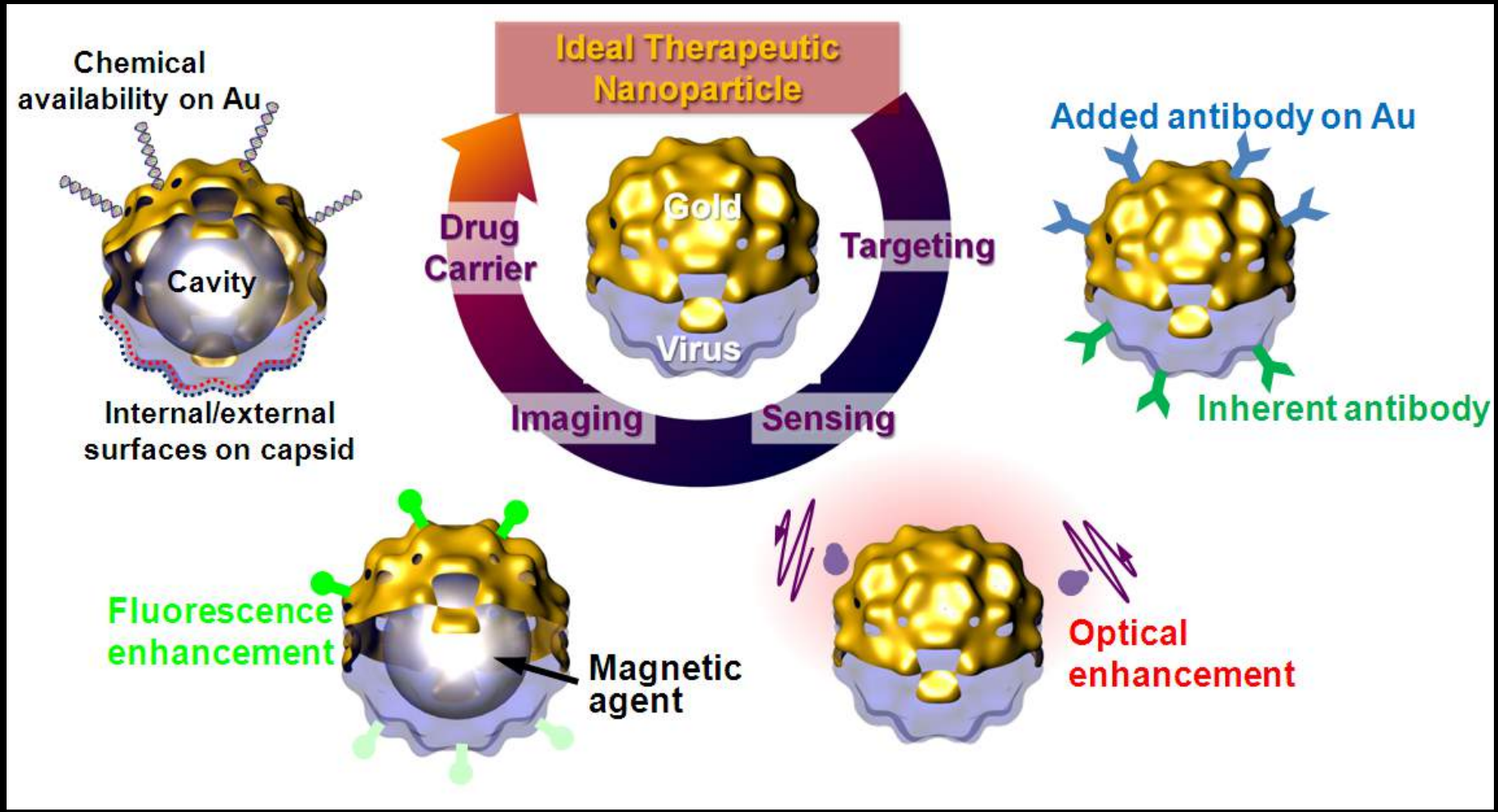


Eu·virus

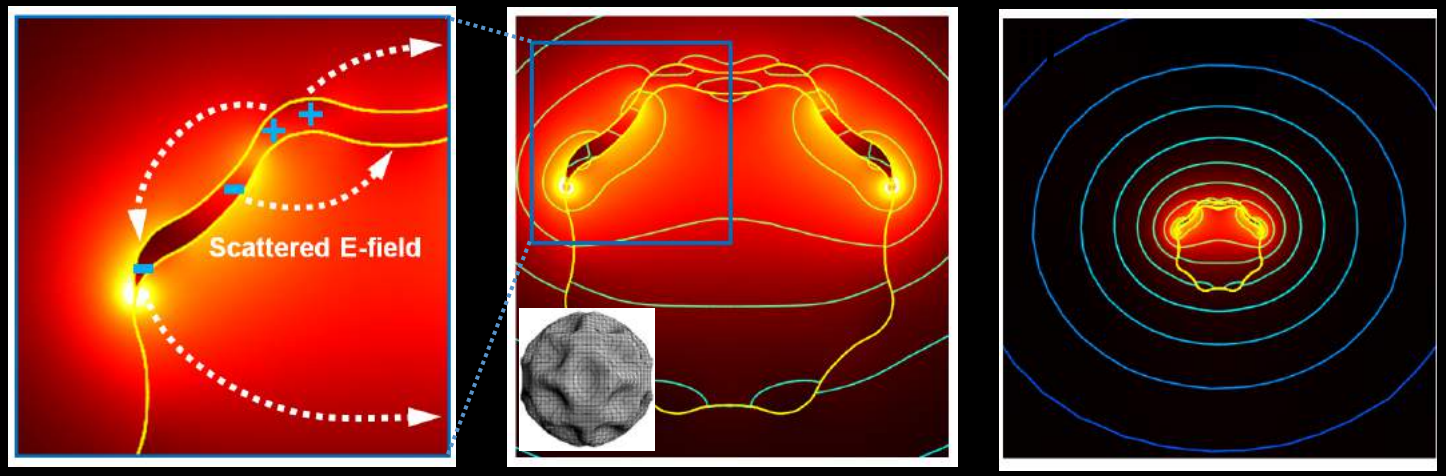
for Targeting, Detection, Gene Delivery, & Regulation in Living Cell: Exploration of Cellular Galaxy

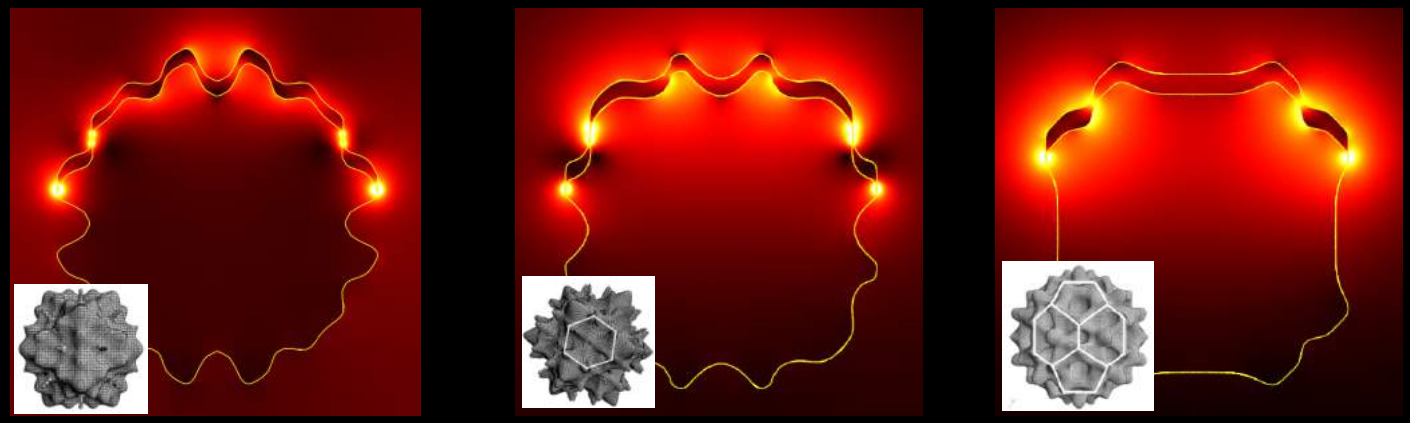
"*eu*" means *good, true, brave, noble, or advantageous*

Multifunctional Eu·virus



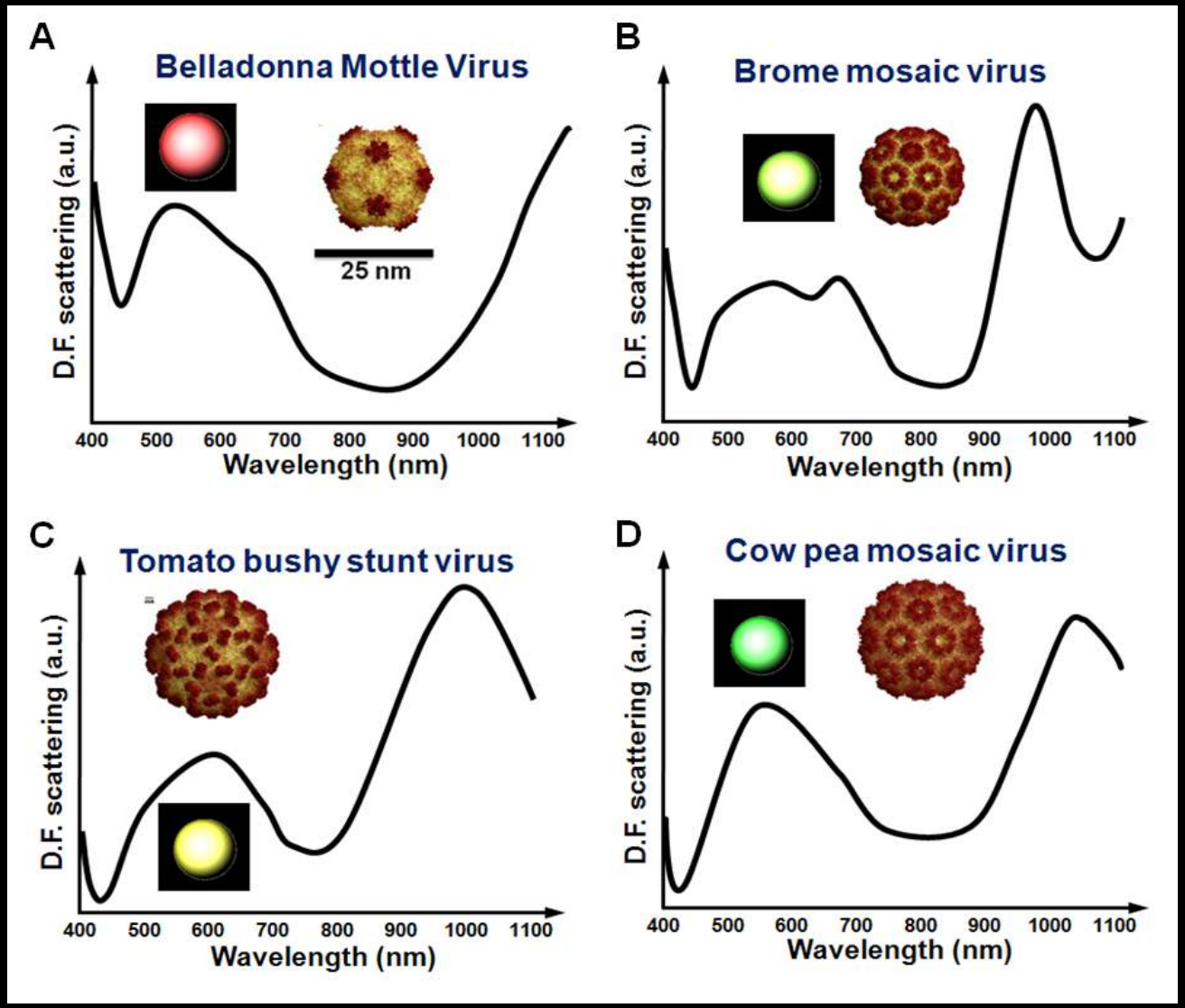
Optical Enhancement of *Eu-virus*



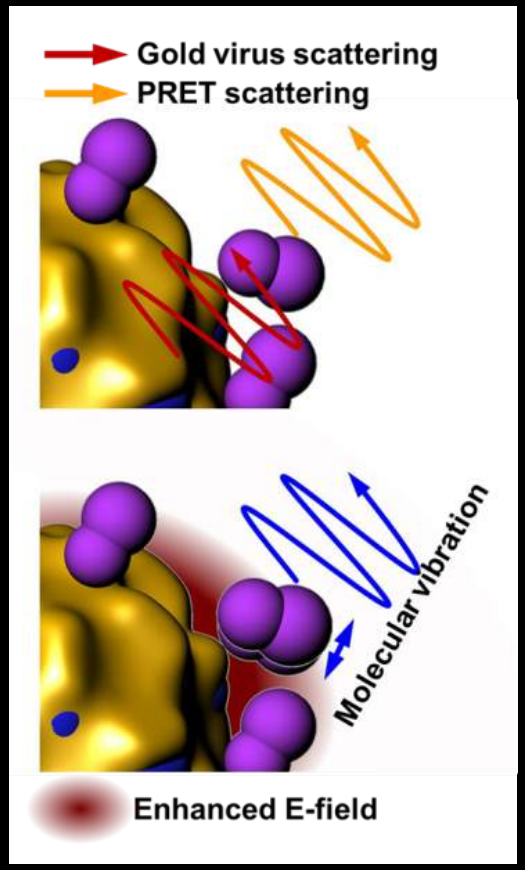


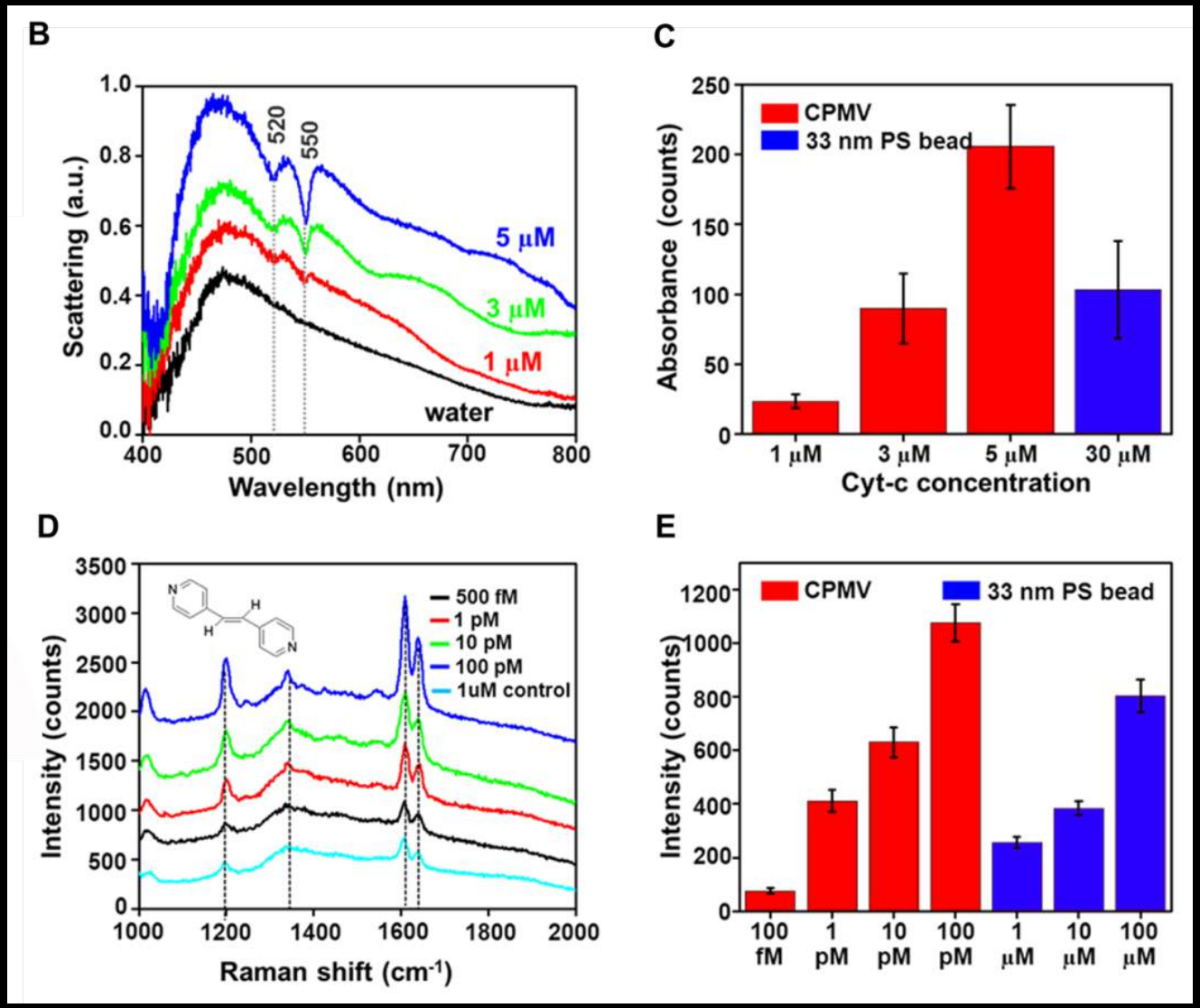
$$P_{Total} = P_{radiative} + P_{resistive} = \oint_S (E \times H) \cdot \mathrm{n}\, dS + \int_V J \cdot E \, \mathrm{dV}$$

Eu·virus Optical Antennas



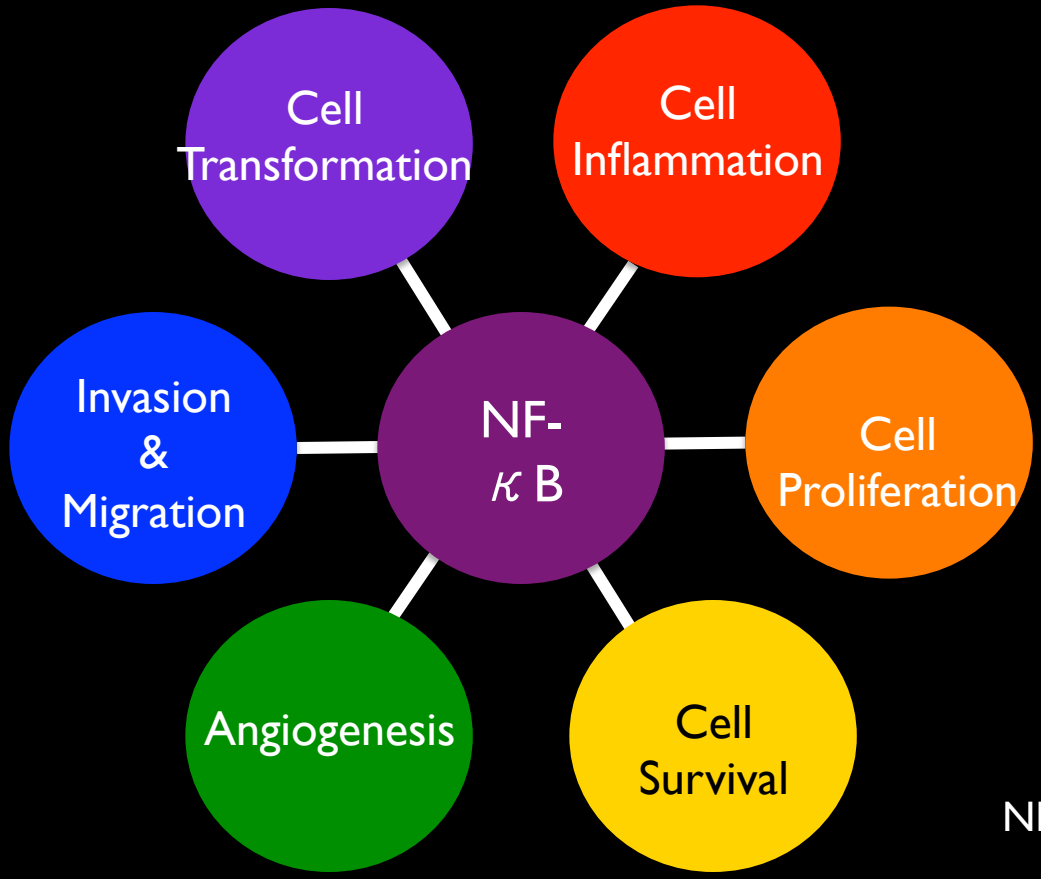
Molecular Imaging via Eu·virus





Photonic Gene Circuit to Control *NF-κB* Transcription Factors

which are persistently active in a number of disease states



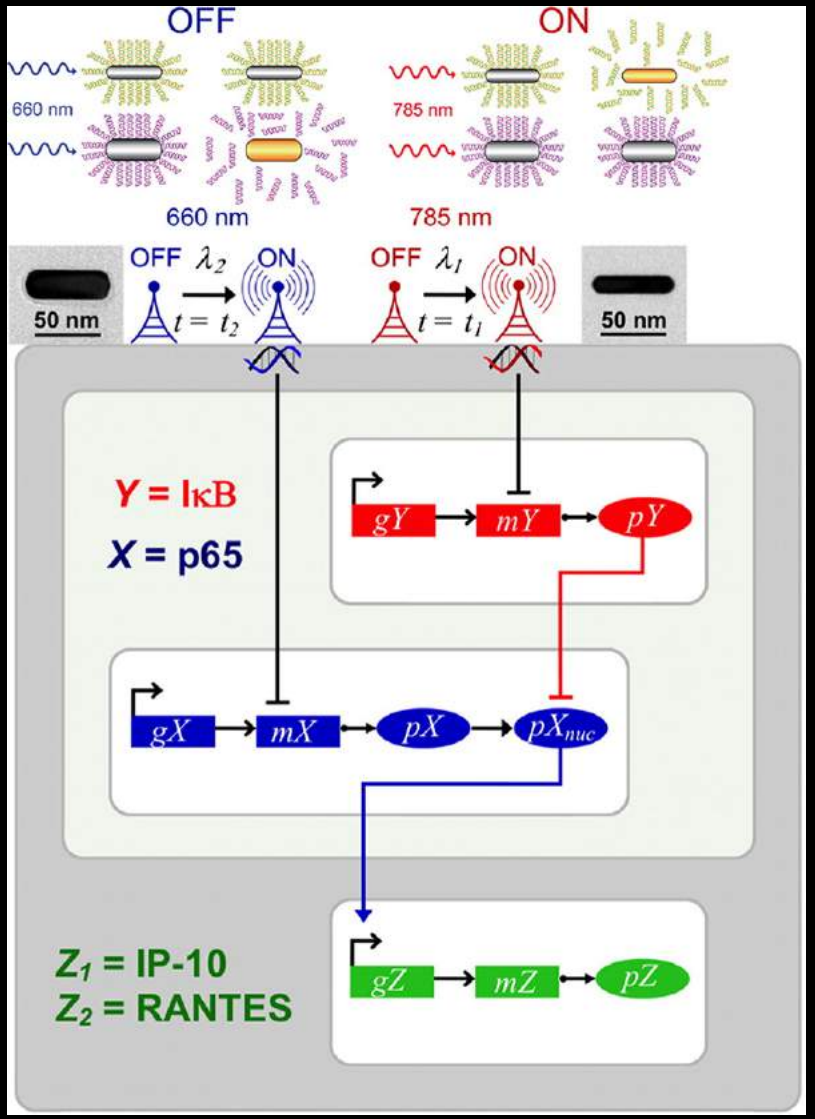
Cancer
Infectious Diseases
Neurodegenerative Diseases
Cardiovascular Diseases
Inflammatory Diseases

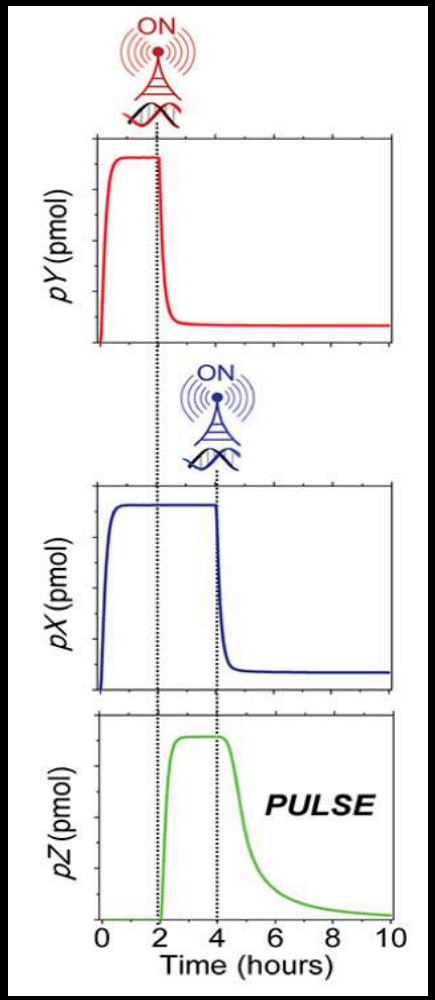
NF-κB: *Nuclear Factor kappa-light-chain-enhancer of activated B cells*

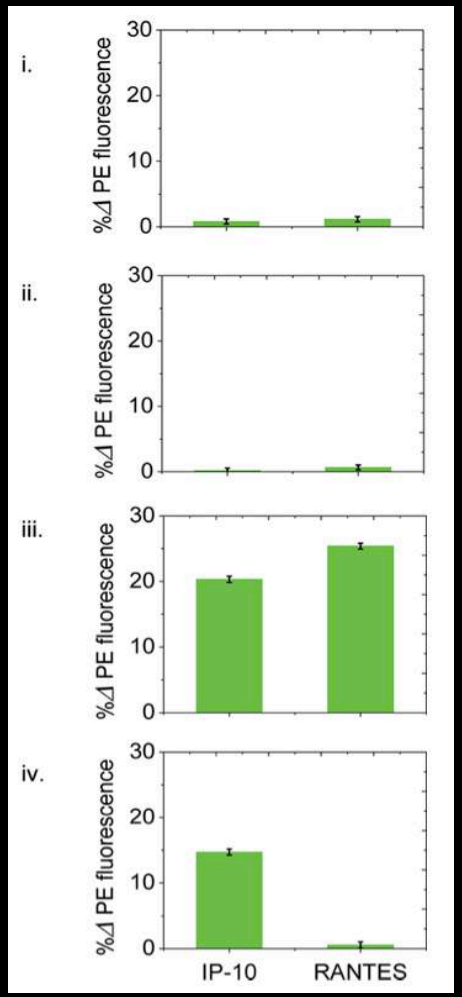
Photonic Gene Circuits

Two NF-κB regulated genes: IP-10 & RANTES

	ON	ON	Output IP-10 *early gene*	Output RANTES *late gene*
i.	0	0	0	0
ii.	0	1	0	0
iii.	1	0	1	1
iv.	1 (t_1 = 0 hr)	1 (t_2 = 2 hr)	1	0





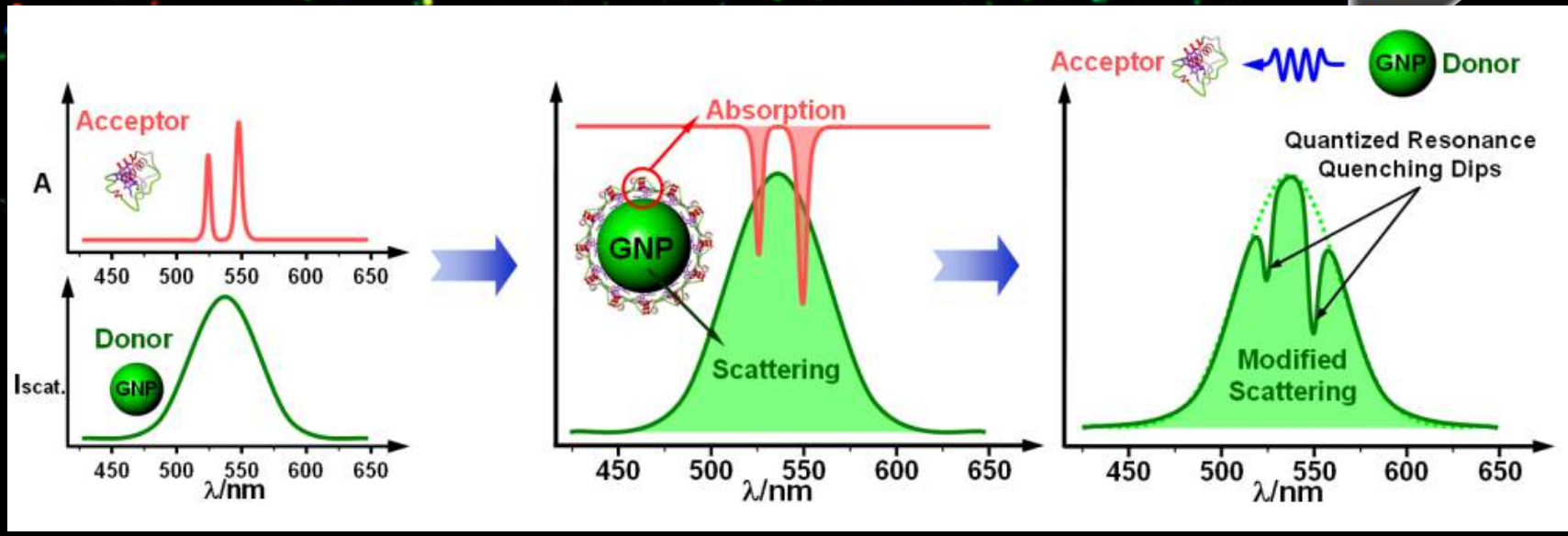


Lee *et al.*, (ACS Nano 2012)

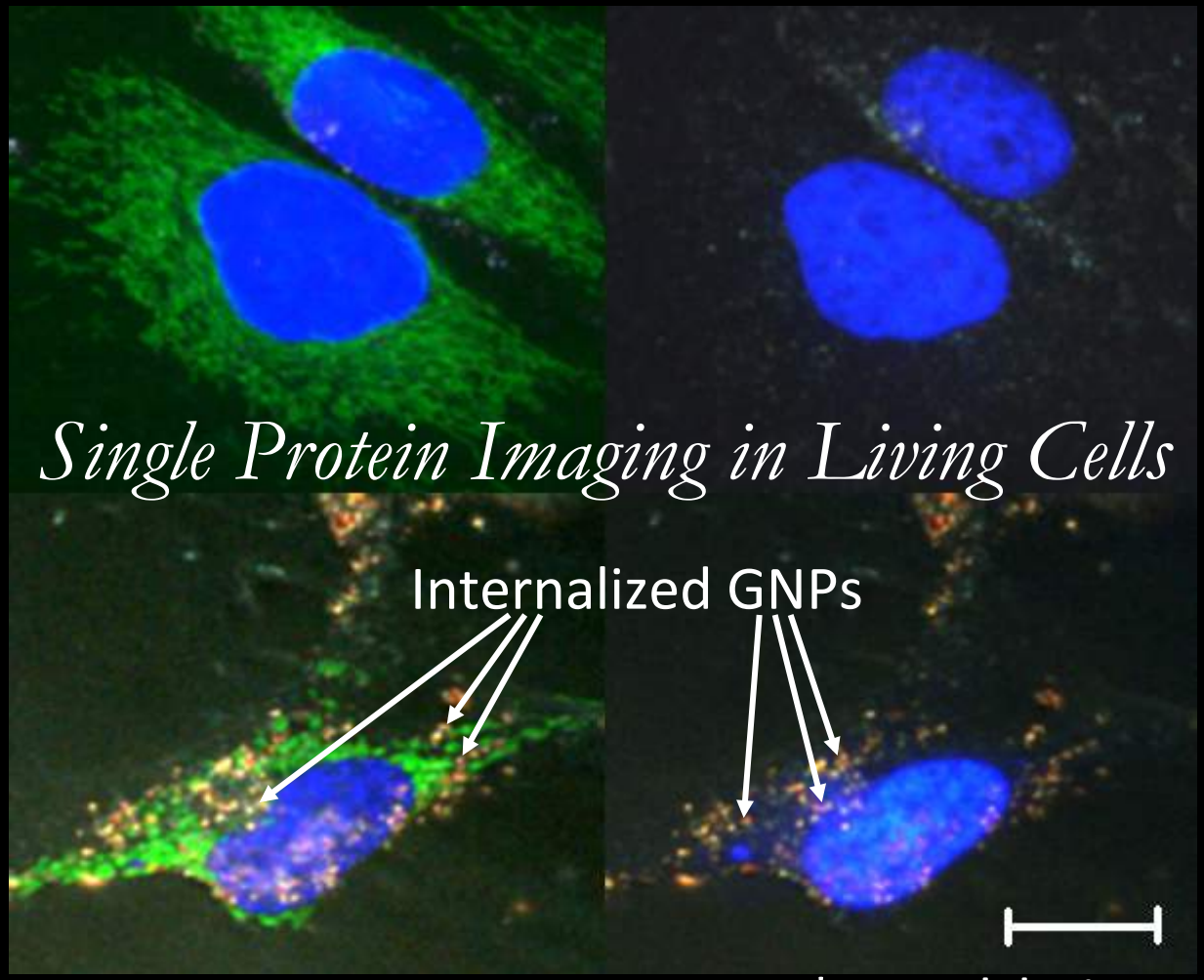
Quantized Nanoplasmonic Dip Spectroscopy by PRET

Quantum Nanoscope

Fiat Lux!



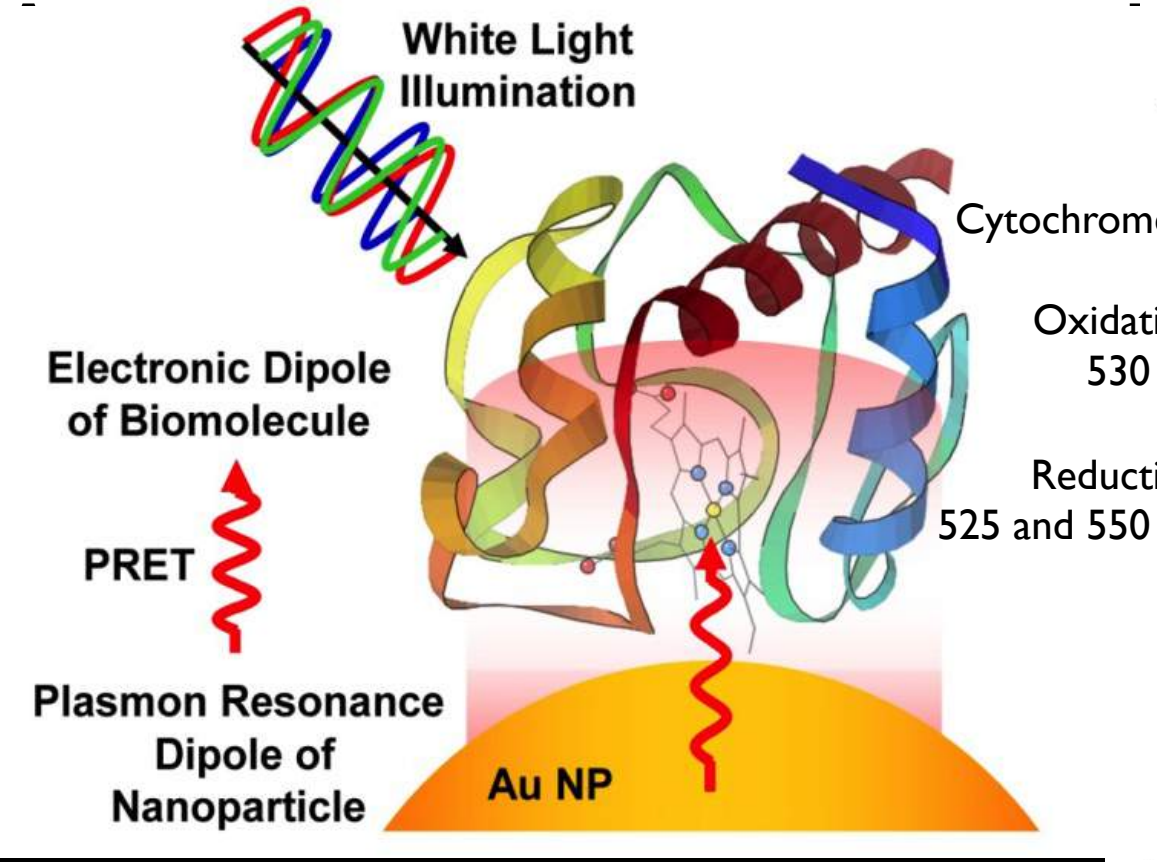
Monitoring Dynamics of Intracellular A*b* Induced Apoptosis in AD*

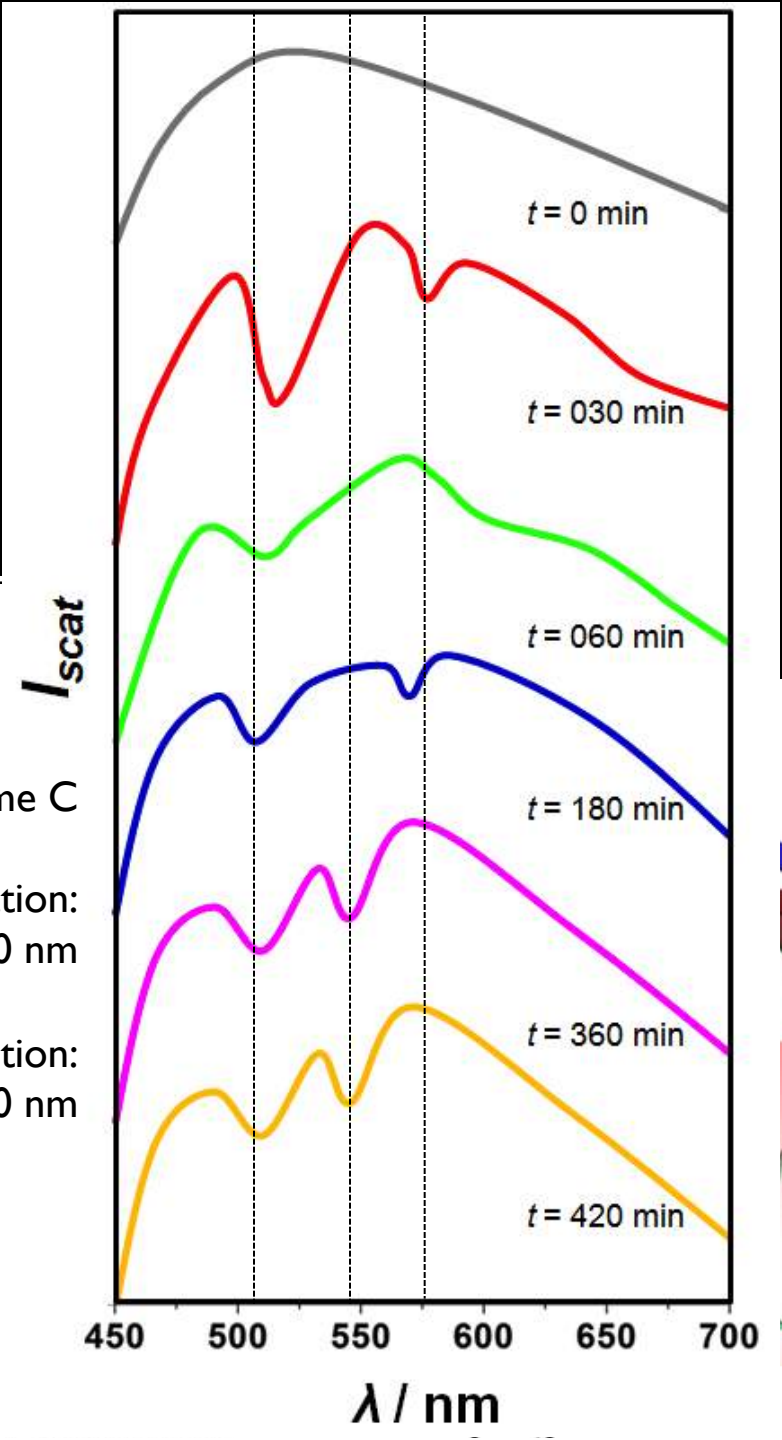


*AD: Alzheimer Disease

Real-Time Observation of Intracellular Cyt c Release *Induced by AβO*

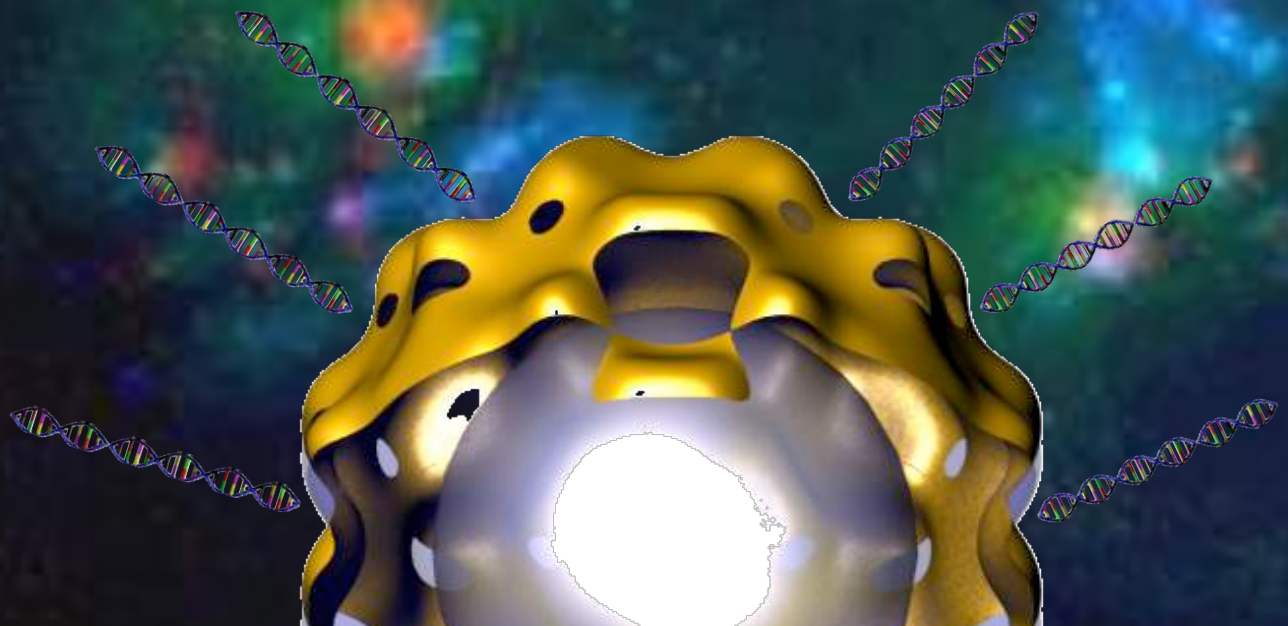
Incubated with AβO (2.5 μM) for 3 hours





Unparallel View of *Cellular Galaxy in Living Cells* via *Nanosatellites*

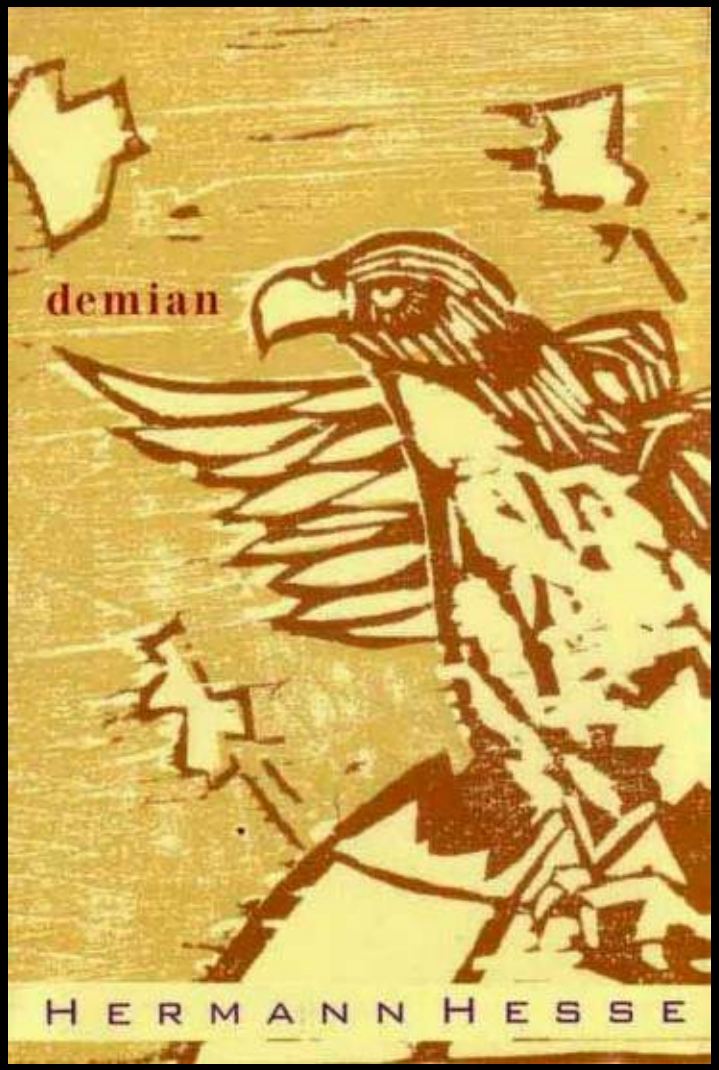
Observations of cellular galaxy can reveal secrets about how cell die, how they disperse molecular dust into the cell, how they transfer electrons in proteins, and the dynamics of life.



Obstacles of Creativity

Rigid structures of

- Educational boundary
- Social boundary
- Political boundary
- Cultural boundary



"Der Vogel kämpft sich aus dem Ei. Das Ei ist die Welt. Wer geboren werden will, muß eine Welt zerstören."

The bird struggles out of the egg. The egg is the world. Whoever wants to be born, must destroy a world.

Conclusions

- Integrated molecular diagnostic systems (iMDx), integrative microphysiological analysis platforms (iMAPs), and nanoscale satellites are developed for precision personalized medicine.
- Precision manufacturing for new medicine will creates healthy economy and new sciences.
- Creative convergence of integrative art, culture, technology, and science (iACTS) can generate healing ecosystem.
- Innovative scale-up manufacturing through the convergence of life science, engineering, and medicine is the solution for global healthcare and healthy economy.

Knowing is not enough;
We must apply.
Willing is not enough;
We must do.

In the realm of ideas
Everything depend on enthusiasm…
In the real world
All rests on perseverance.

Johann Wolfgang von Goethe

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