Nanotechnology – The Enabling Tool for the 21st Century

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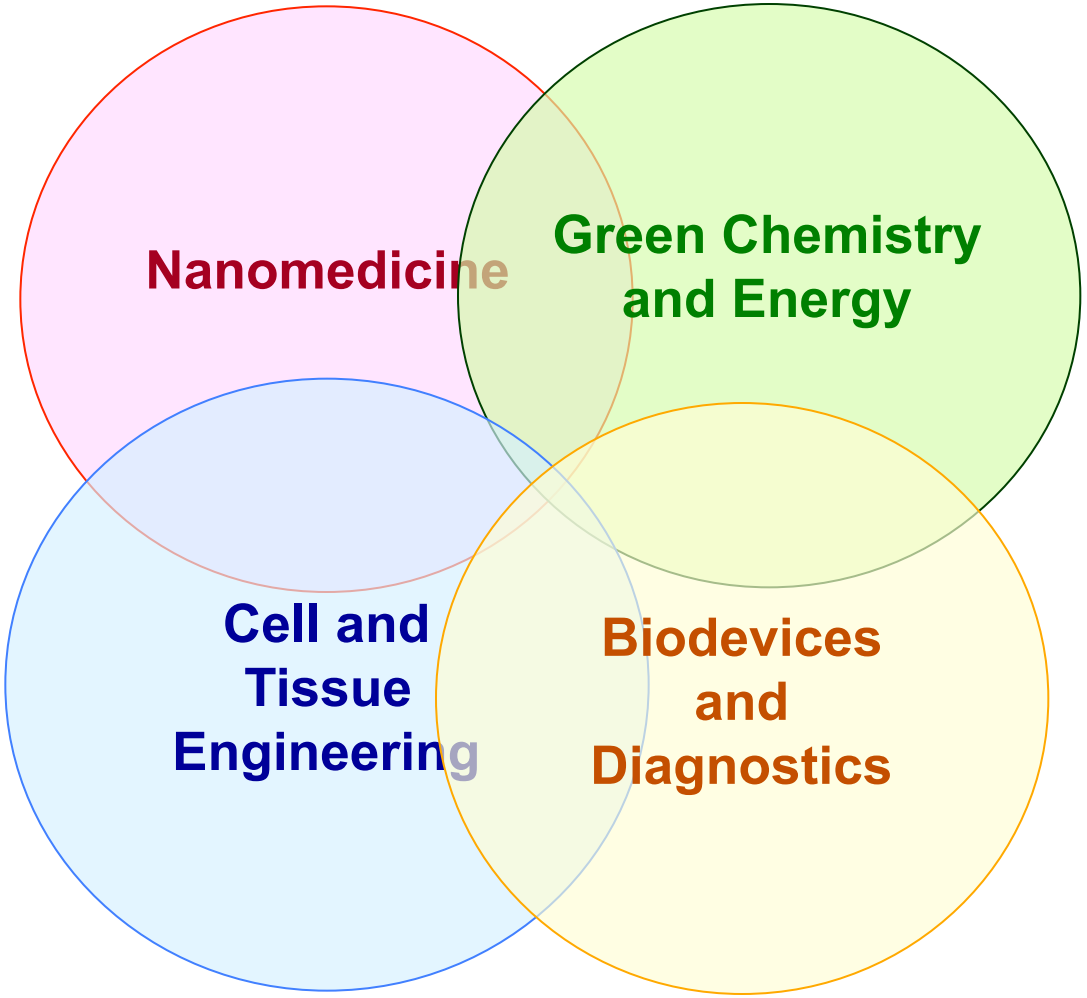
Research at the Interface of Bioengineering and Nanotechnology



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IBN's Mission

- Create new fundamental and industrially relevant knowledge and technologies
- Make a translational impact with our technology platforms via strong clinical collaborations

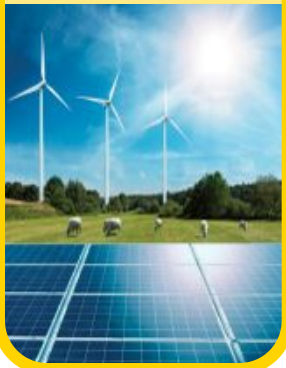
Pharma

Medical Technology

Consumer Products

Food, Nutrition

Clean Tech



Chemicals

- Contribute towards the economy through technology commercialization via MNC partnerships and spinoffs

- 974 Publications • 502 Active Patents/ Patent Applications • 7 Spinoffs

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Grand Challenges for the 21st Century

14 Grand Challenges in Engineering to Impact
Sustainability, Health, Vulnerability, and Joy of Living

www.engineeringchallenges.com
National Academy of Engineering, U.S.A.

- Early Diagnosis of Diseases → Nanodevices
- Engineering Better Medicine → Nanomedicine
- Provide Access to Clean Water → Nanoporous Membranes
- Sequestration of Green House Gases → Nanocatalysts
- Making Solar Energy Economical → Nanocomposites

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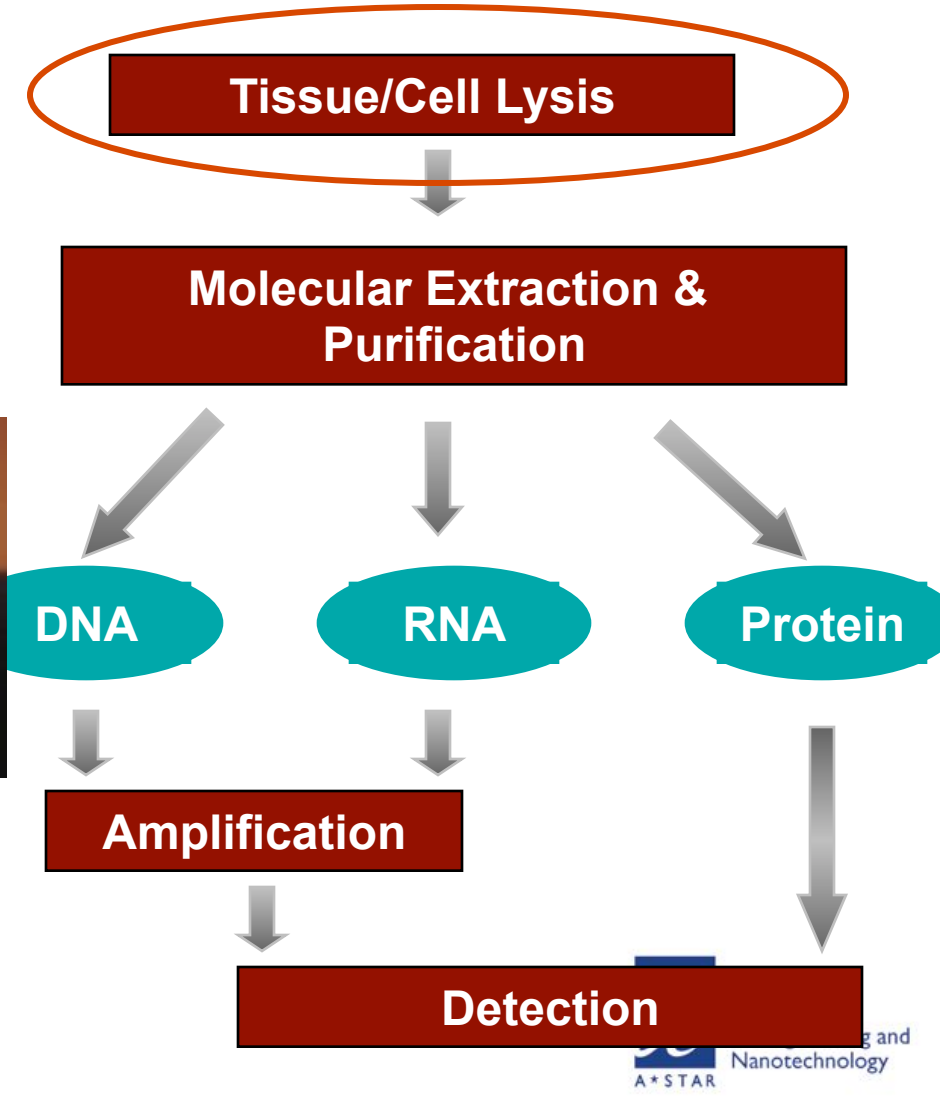
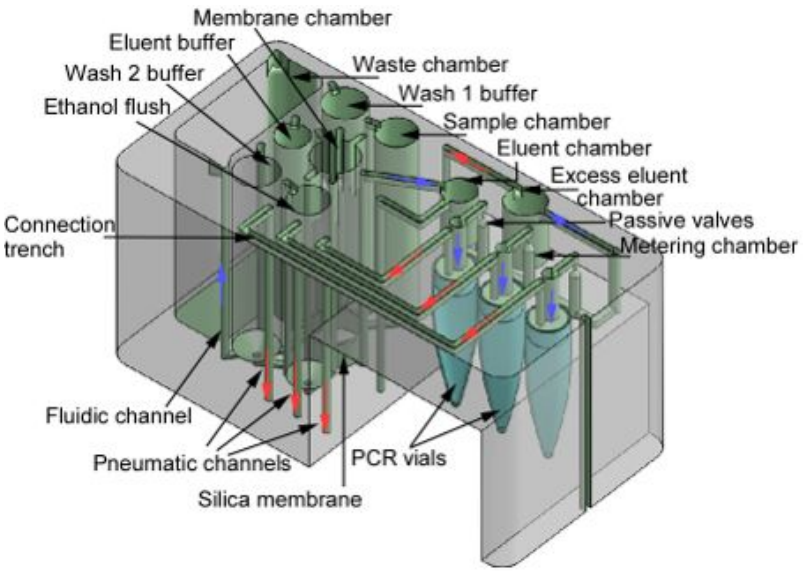
Molecular Diagnostics Systems

Challenge – Rapid, accurate diagnosis of infectious diseases (Market: $2.1B)

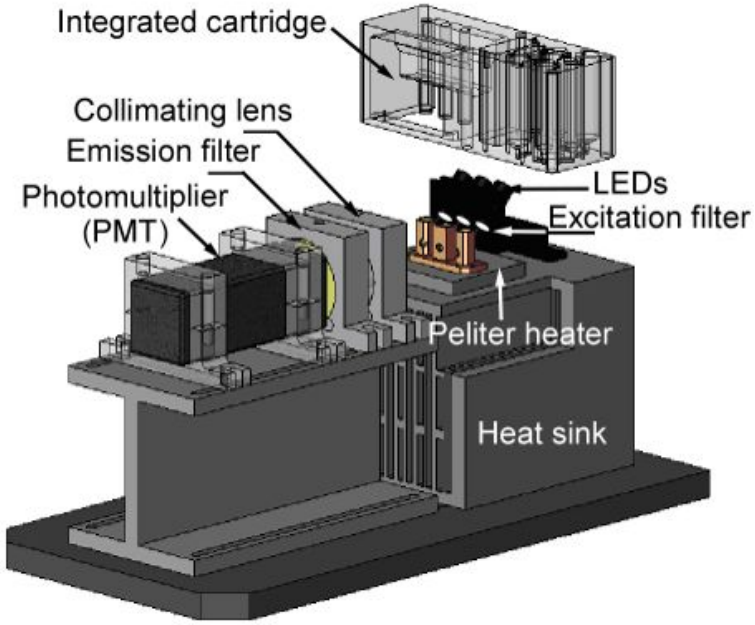
Biosample Preparation and Analysis



MicroKit for Automated Disease Diagnosis



Test cartridge with pre-loaded reagents



Automated detection system

- Fully automatic lab-on-cartridge system with RNA/DNA extraction and 3-channel real-time PCR for rapid disease diagnosis
- Rapid sample preparation and diagnosis (≤ 2 h)
- Disposable polymer cartridge (< $1) with self-contained reagents
- A compact desktop system for hospitals, clinics and checkpoints

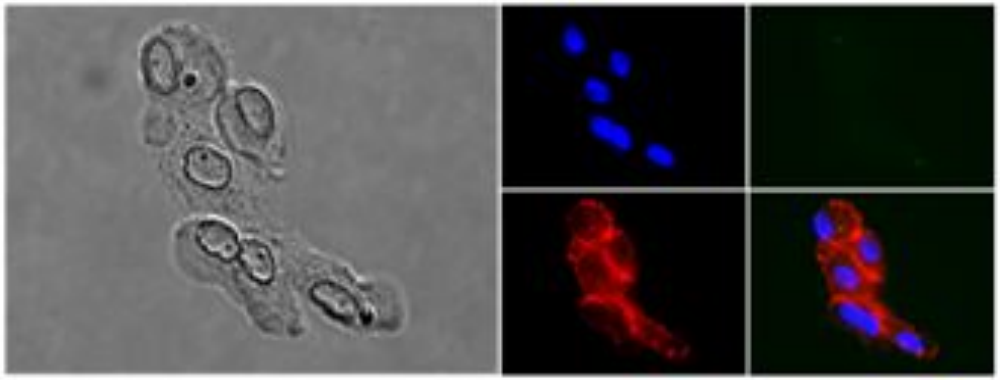
Successfully demonstrated for influenza typing and sub-typing

SG Molecular Diagnostics WSJ Asian Innovation Silver Award

A*STAR Nanotechnology

Cancer Diagnosis

Problem – Difficult and expensive to perform cancer diagnosis and prognosis



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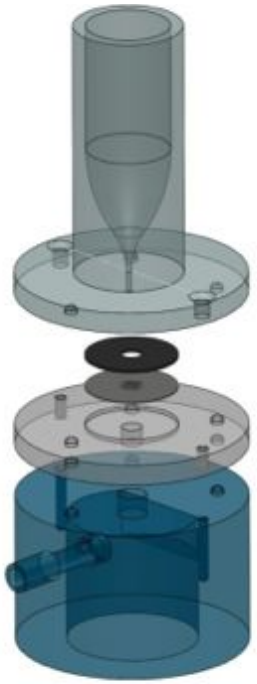
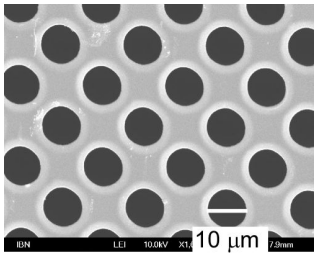
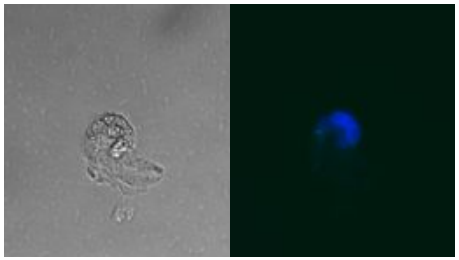
Circulating Tumor Cells (CTCs)

- A 'liquid biopsy' → Isolation of rare CTCs from peripheral blood for cancer diagnosis, monitoring
- Microsieve fluidic device provides excellent and much more rapid CTC recovery
  → Superior to commercial FDA-approved devices
- A fully automated system for isolation, enumeration, and biomarker analysis of CTCs
  - Non-invasive, near real-time, inexpensive, accurate personalized cancer management
  - Single cell analysis → new biomarker

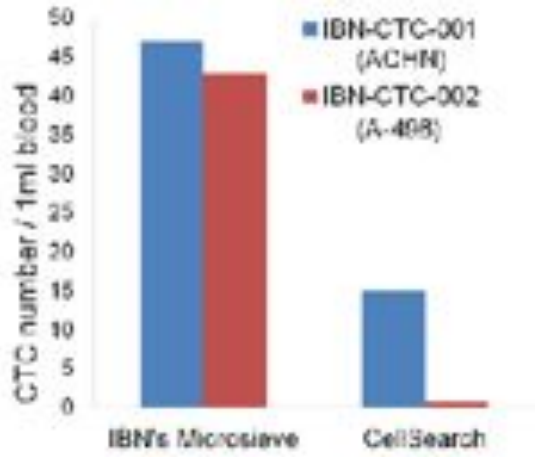




Microsieve



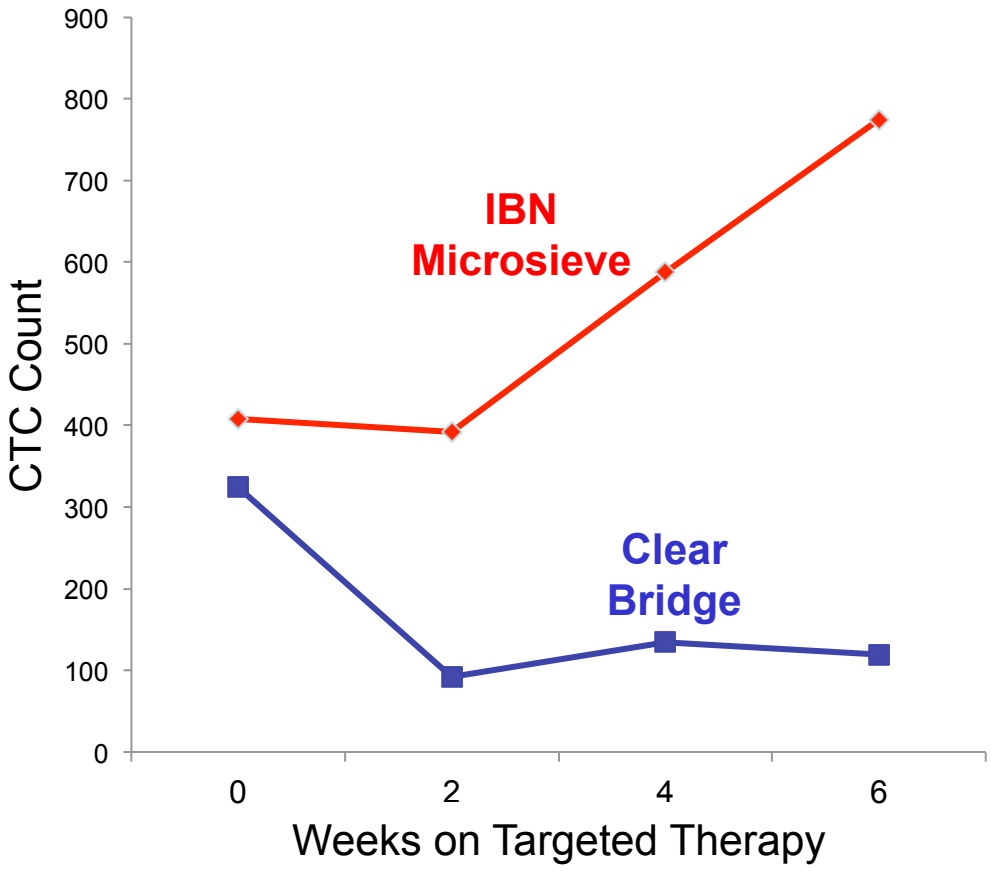
Single isolated CTC



Real World Comparisons

Case Study: Patient Receiving Futile Targeted Therapy

→ Detected successfully by IBN Microsieve



Enlarging Brain Metastasis on Futile Therapy

Baseline

Post-Therapy

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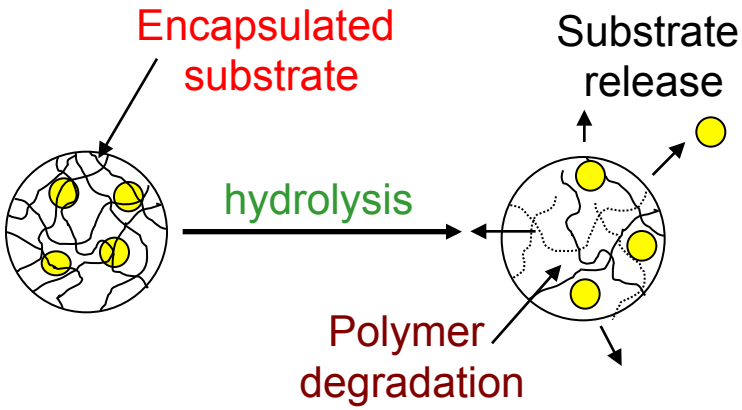
Stimuli-Responsive Drug Delivery Systems



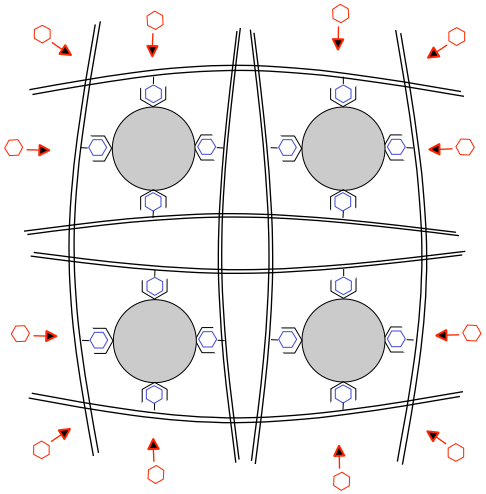
Conventional Release Mechanism

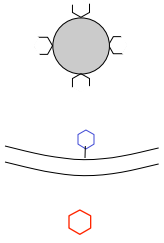
- Constant or exponential release over time
- Responsive to pH or temperature change

Need for Stimuli-Responsive Drug Delivery

- Insulin delivery to patients with diabetes mellitus
  - Insulin release in response to glucose concentration
  - Mimic physiological secretion
  - Eliminate the need for patient blood sugar monitoring

Glucose-Sensitive Polymers





Tetravalent glucose-binding protein (e.g. Con A)

Polymer containing glucosyl groups (e.g. Dextran)

Free glucose in blood stream

Tailoring of Insulin Delivery Nanoparticles

Glucose-sensitive polymers as insulin carrier

Protect insulin to enable oral or nasal delivery

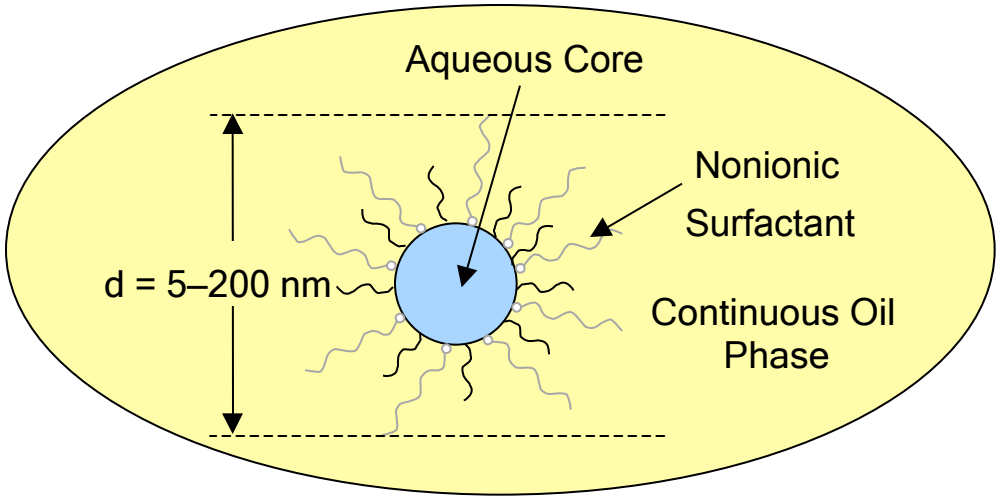
Degrade only at high blood glucose concentration

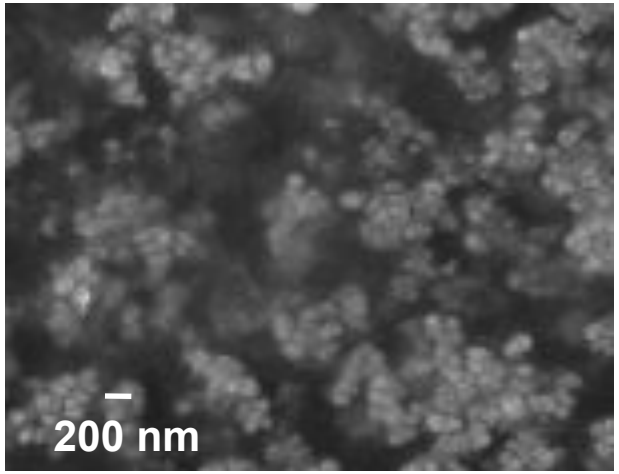
Insulin released upon polymer degradation

Formulation of polymer as nanoparticles – Reverse Microemulsion

Small enough to escape macrophage digestion

Enhance systemic absorption/bioavailability

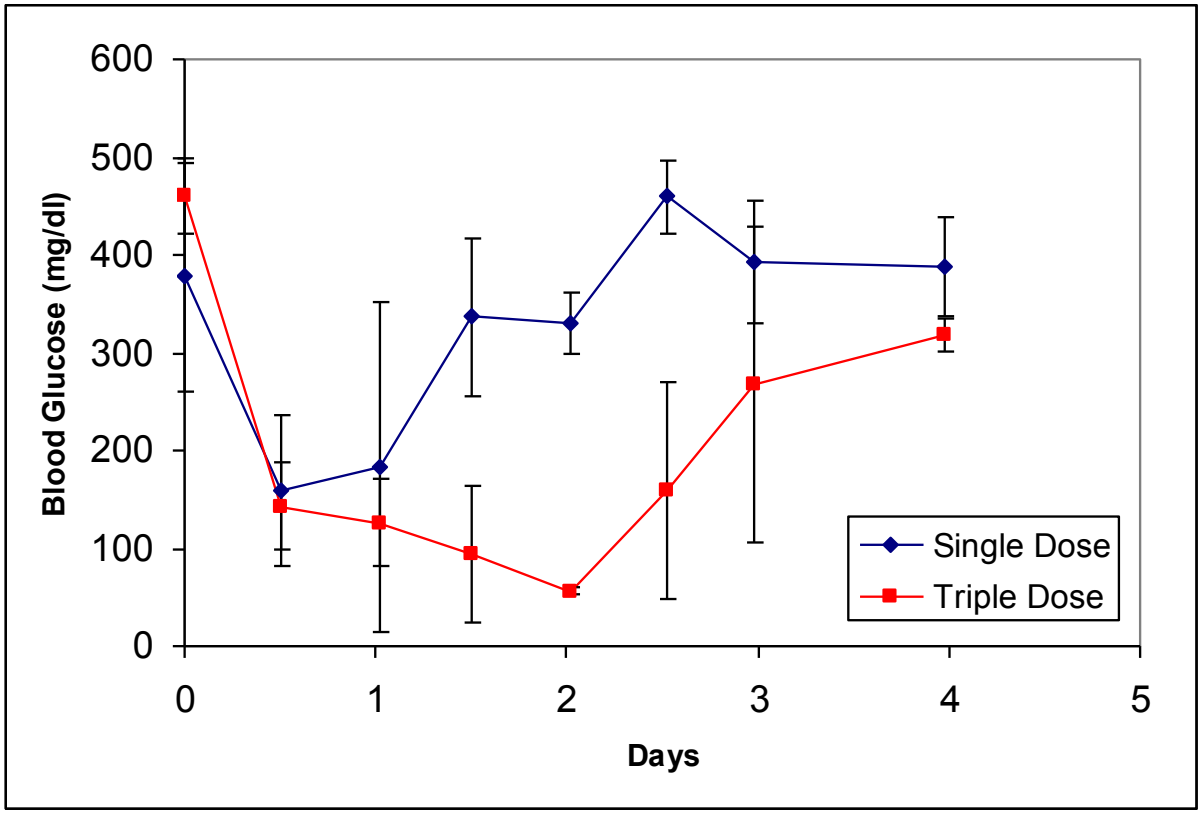




In Vivo Bioactivity

- STZ-induced diabetic rats allowed to eat *ad libitum*
  - Dextran-insulin gels lower glucose *in vivo*
  - Increased dosage provides longer control

SmartCells, Inc.



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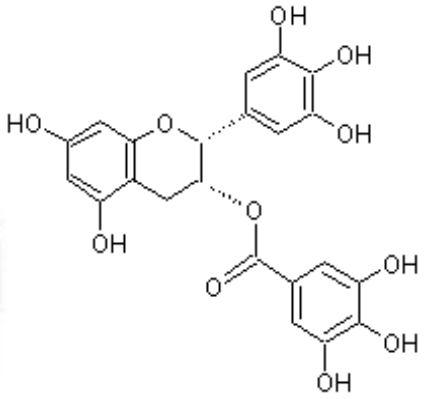
Green Tea Drug Carriers with Synergistic Effects

What if the drug carrier also provides therapeutic effects?

- The drug ratio of carrier is no longer a restrictive issue
- Synergistic therapeutic effects between the carrier and the drug

EGCG as drug carrier

Green tea



Epigallocatechin-3-gallate (EGCG)

- Major constituent of green tea
- Anti-cancer, anti-oxidant, anti-inflammatory, anti-microbial and anti-aging activities
- High binding affinity to protein due to π-π stacking interactions between EGCG and amino acid with ring structure in protein

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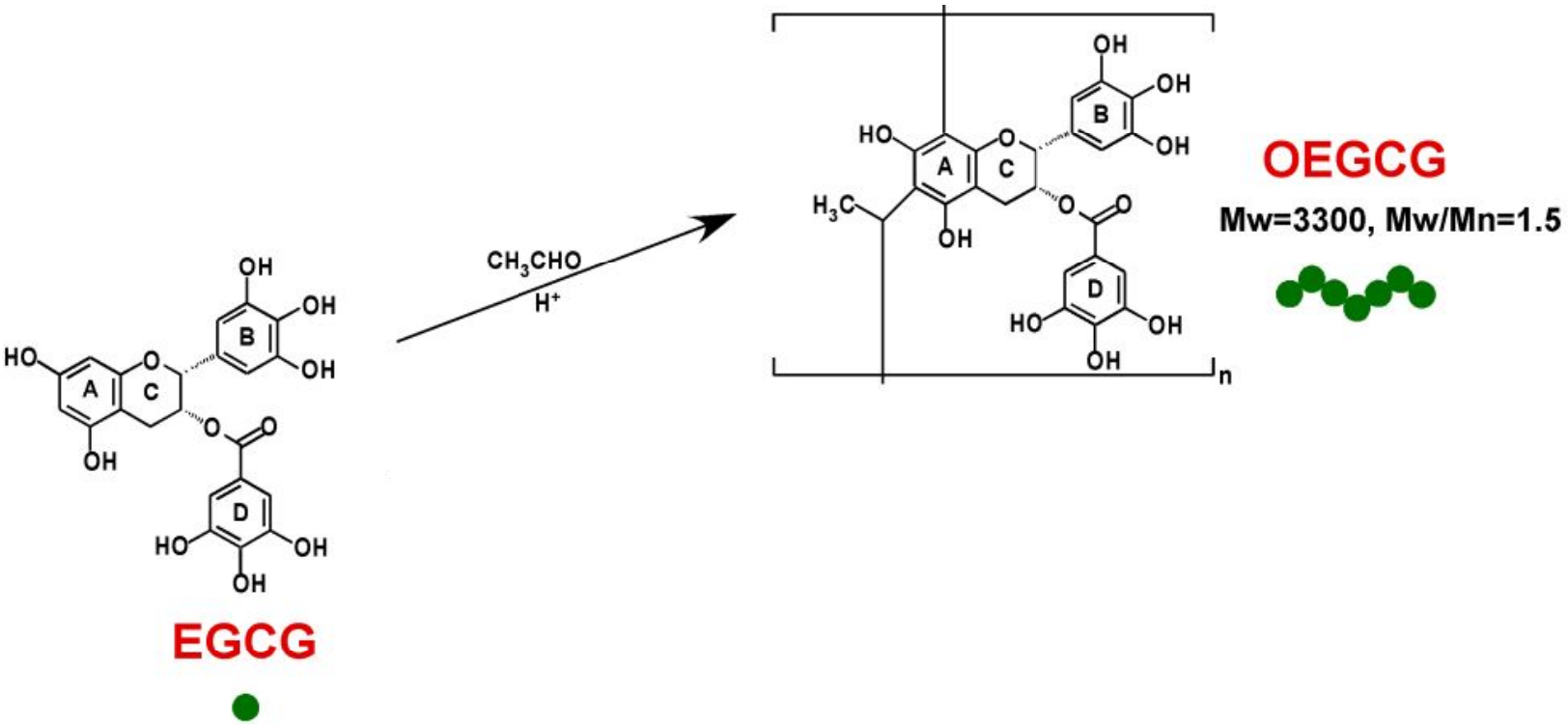
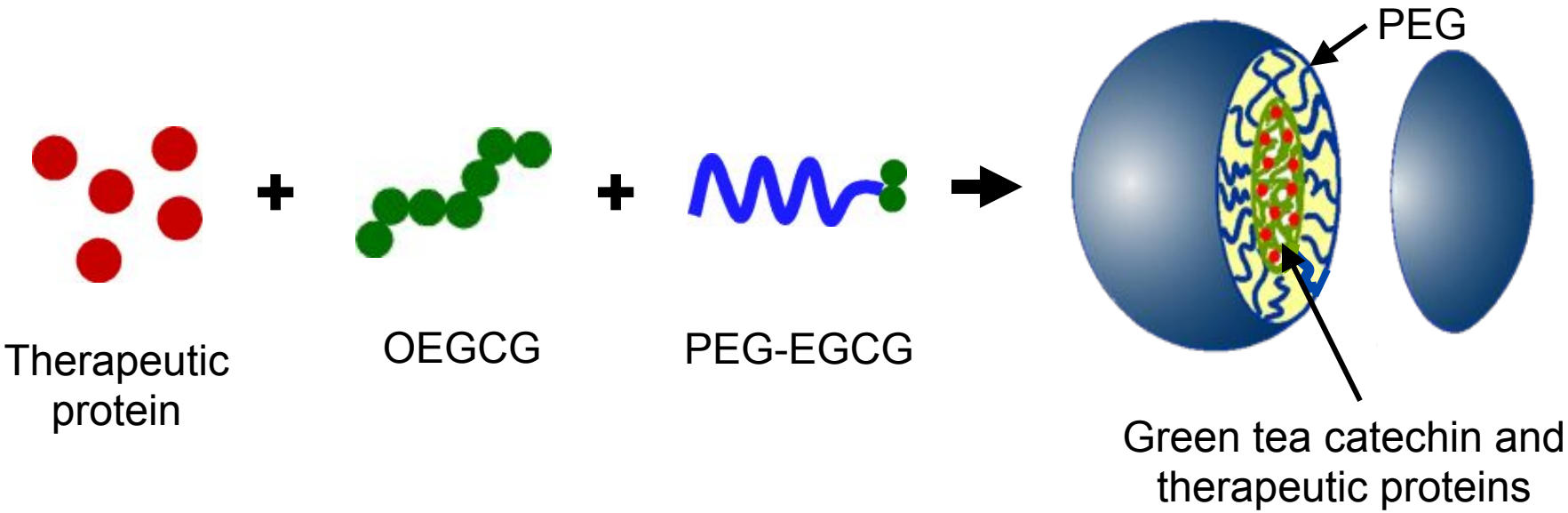
Synthesis of EGCG Derivatives



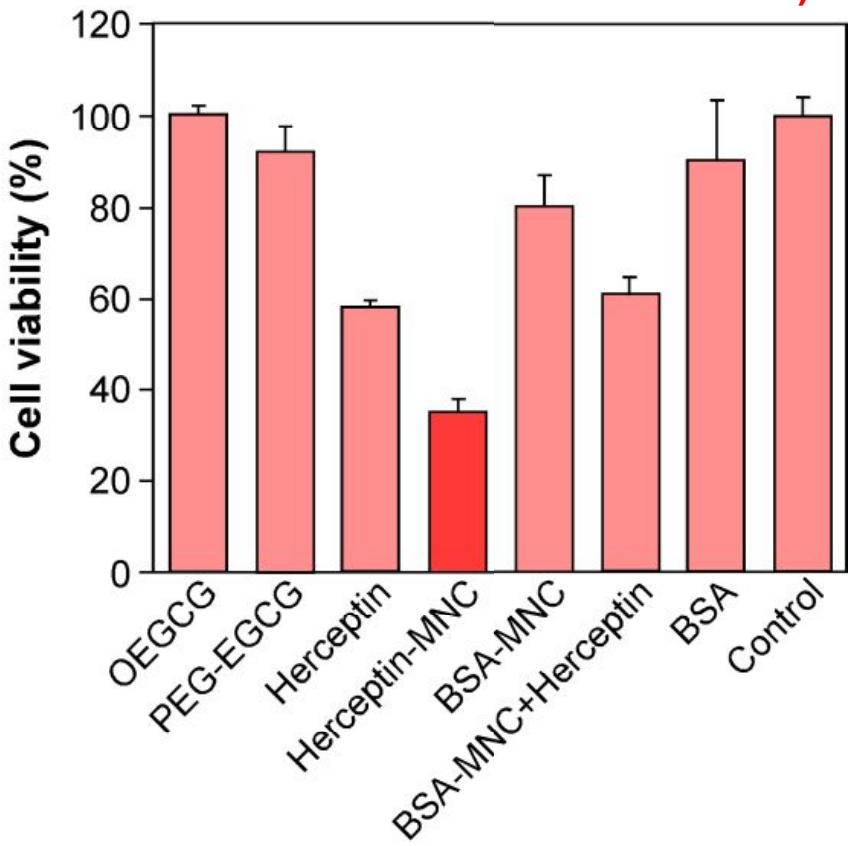
Self-Assembly of Green Tea Nanocomplex



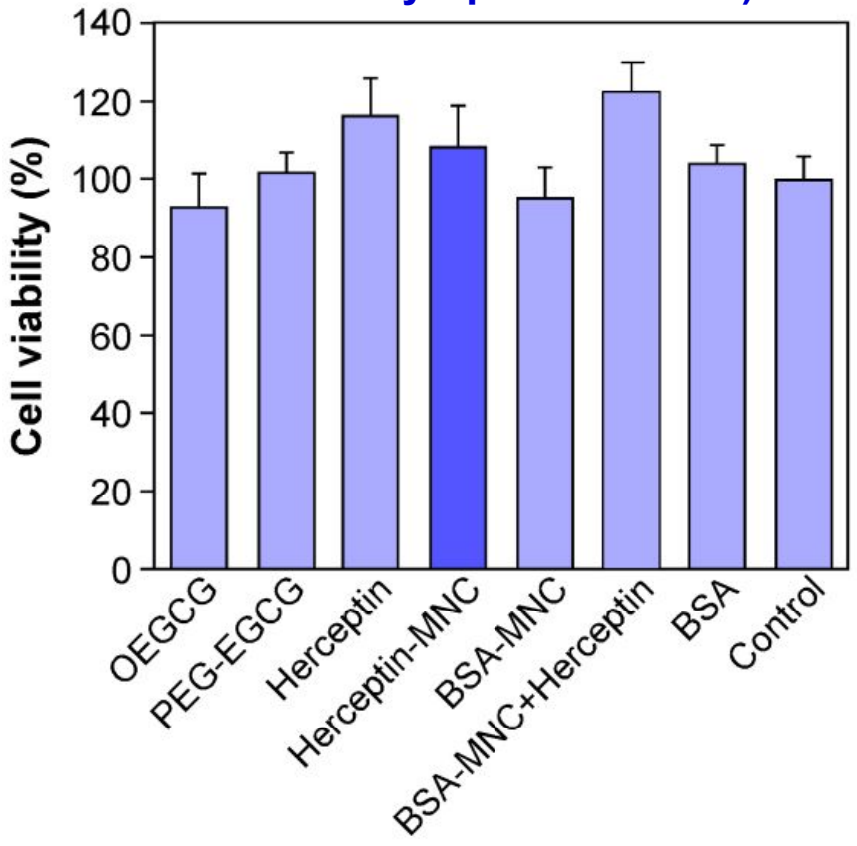
- Oligomeric EGCG (OEGCG) – Stabilizes micelle formation
  – Higher cancer cell growth inhibition effect than EGCG molecule
- PEG outer shell and tailored nano size
  – Long circulation and passive tumor targeting
- Proteins are protected from rapid proteolysis and renal clearance
- Synergistic anti-cancer effect between proteins and EGCG derivatives

Green Tea–Herceptin Micelles for Cancer Therapy

BT-474 (HER2-Overexpressing Human Breast Cancer Cell Line)



HMEC (Human Normal Mammary Epithelial Cells)



- Herceptin targets HER2-overexpressed BT-474 breast cancer cells
- Green tea-Herceptin micelles – Superior to Herceptin alone
  – Inhibit only cancer cell proliferation *in vitro*

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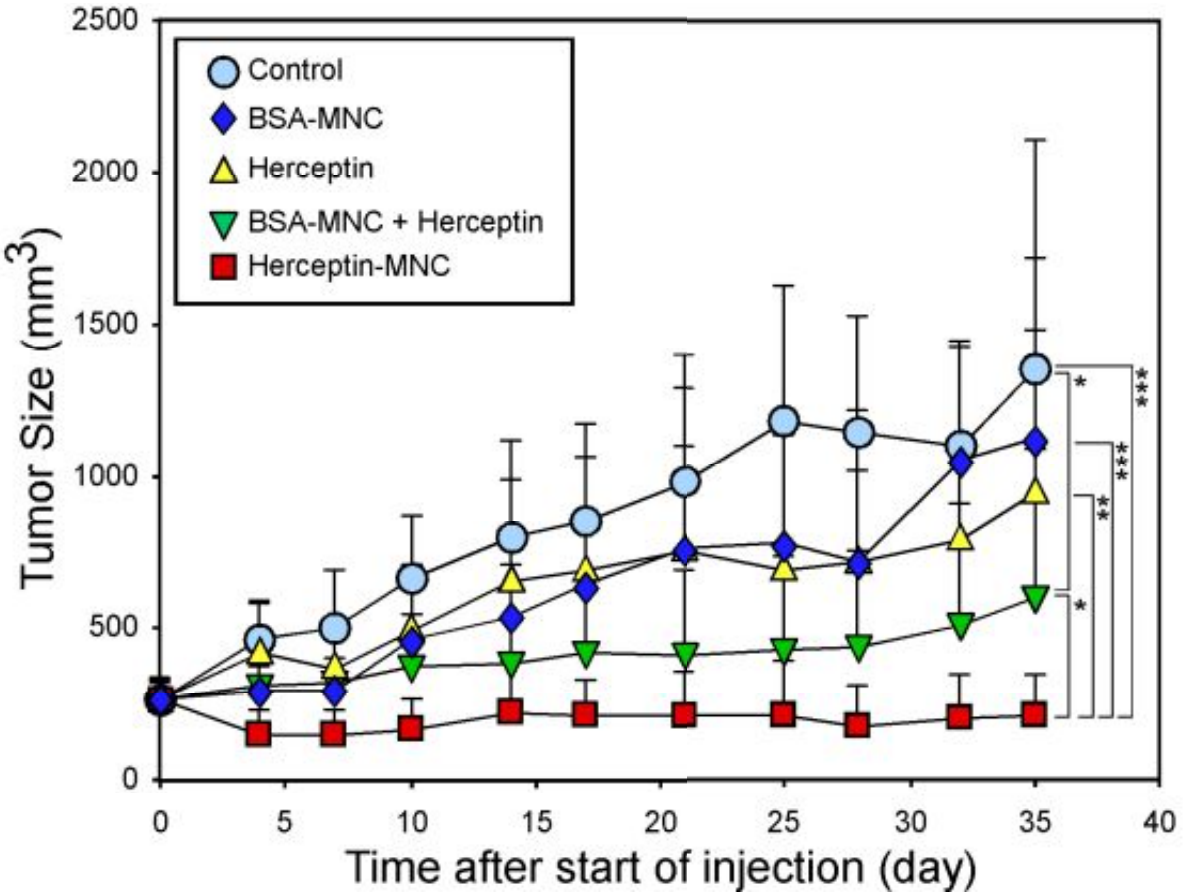
Anticancer Effect on BT-474-Xenografted Mice



*p < 0.05
**p < 0.01
***p < 0.0001

Nature Nanotechnology (2014)

- Green tea-Herceptin micelles
  - Retard tumor growth *in vivo*, induce cell death in tumor
  - Greatly enhance the anti-cancer efficacy of Herceptin

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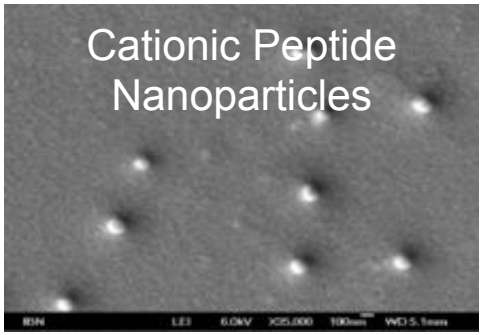
Antimicrobial Agents

Challenge – Drug resistance develops with use of conventional antibiotics

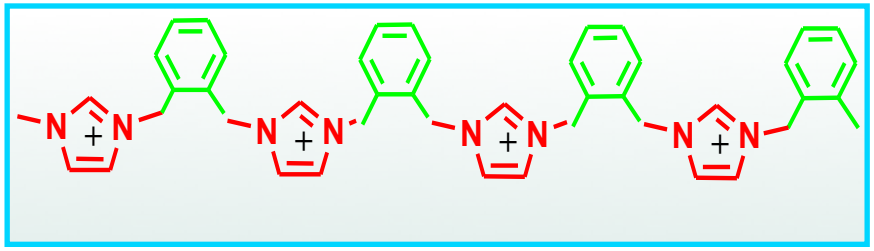
- Over 90,000 deaths/yr in the U.S. can be attributed to bacterial infections
- Overuse/misuse of broad-spectrum antibiotics → Rise in “superbugs”
- MRSA → Almost half of all skin infections
- Bioflims – Bacteria formation on surfaces of implanted devices and facilities
- 42,000 nosocomial infections/yr (U.S.) → $43K/person (added healthcare cost)
- Treatment cost: $40B in 2010 (global)
- Global market for personal care: $10B
- Due to lack of new discoveries, FDA has offered to fast-track new antibiotics

Novel Antimicrobial Agents



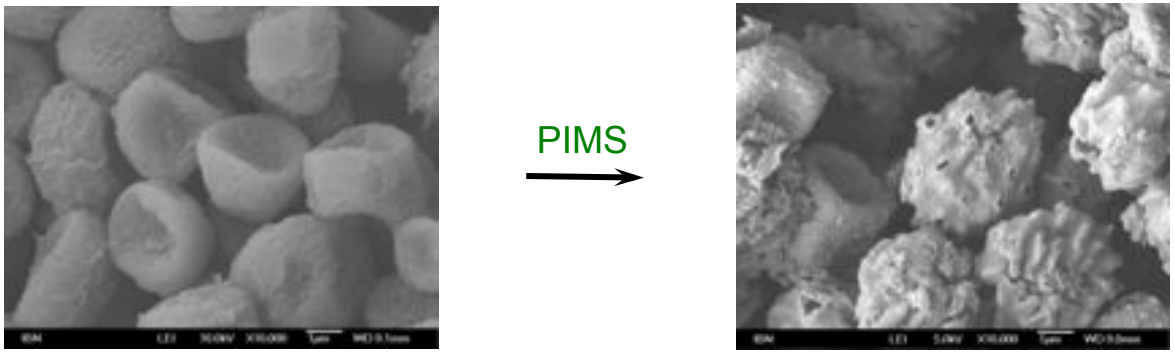
Nature Nanotech. (2009)

Polyimidazolium Salt (PIMS)



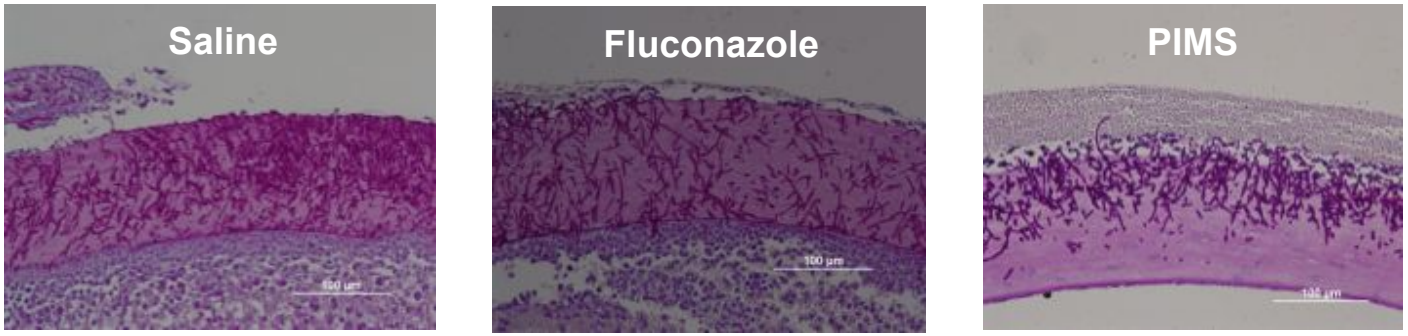
Nano Today (2009)

Polyimidazolium Salts as Antimicrobial Agents



- PIMS destroys *Niger* membrane, lysing the fungi cells and preventing the cells from developing resistance

Successful Fungal Keratitis Treatment by PIMS



Biomaterials (2013)

- PIMS reduces the maximal depth of hyphal invasion into cornea, significantly decreasing the counts of *C. albicans*, as compared to saline and fluconazole

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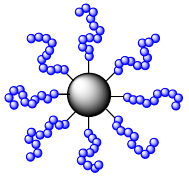
Macromolecular Antimicrobial Agents

- Broad spectrum activity *via* membrane disruption
- Rapid killing of microbial pathogens
- Precludes development of resistance
- Non-toxic, no skin irritation
- Biodegradable, eco-friendly
- Lysis of biofilm
- Low cost, scalable

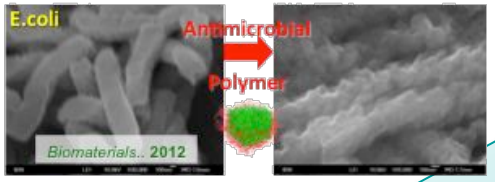
Anti-TB



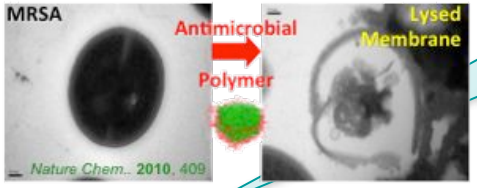
Biofilm Prevention

Cream and Hydrogels

Gram Negative Bacteria

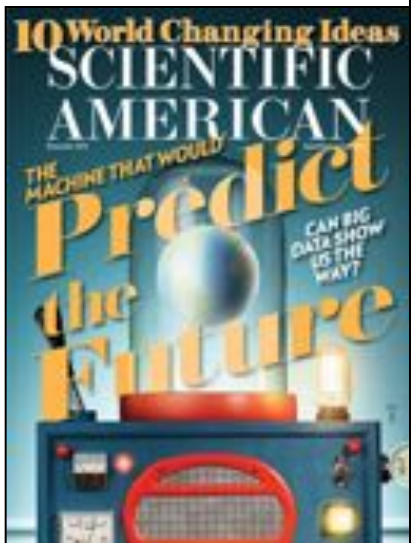


Gram Positive Bacteria/Fungi

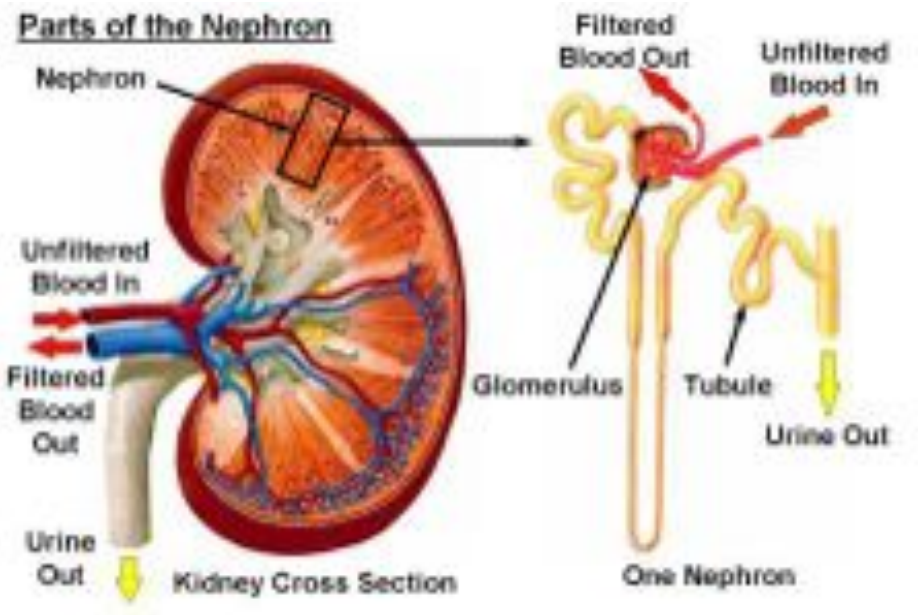


Applications

- Anti-MRSA, anti-TB
- Disinfectant, preservatives in personal care products



Functional Morphology of the Kidney



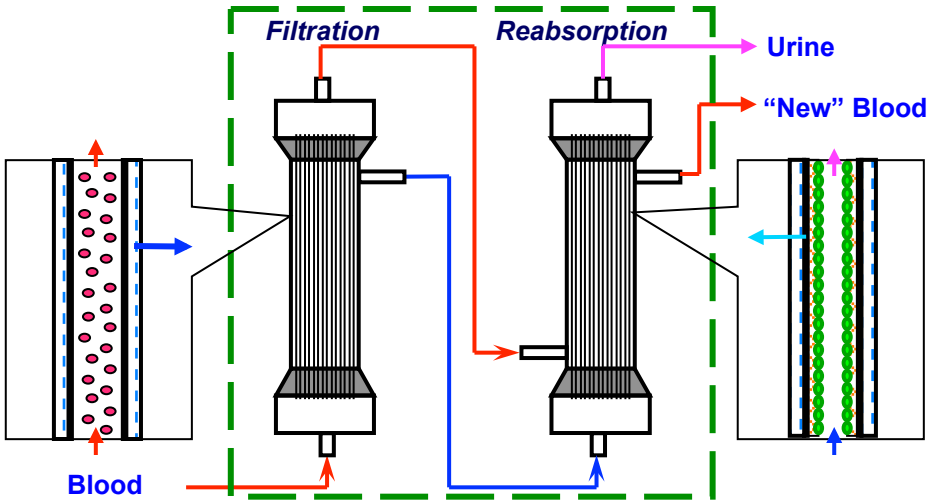
Gomerulus

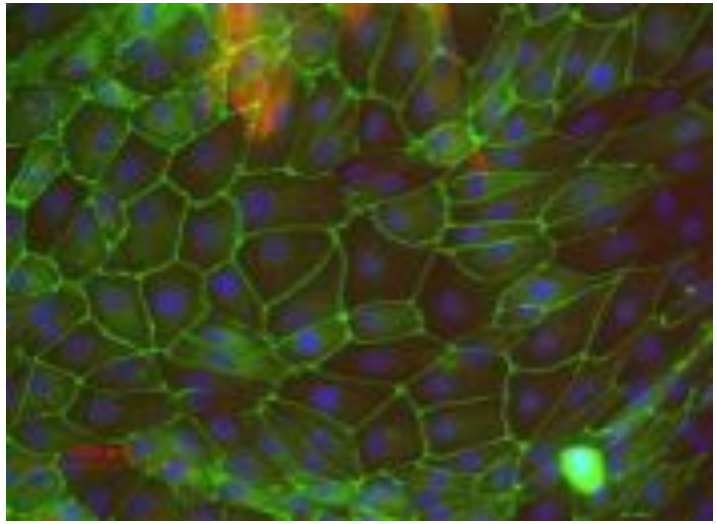
- Hemofiltration

Proximal Tubule

- Reabsorption of glucose, amino acids, sodium, bicarbonate, etc.
- Secretion of creatinine, uric acid, antibiotics, xenobiotics, etc.
- Immunomodulatory functions
- 1,25-dihydroxy vitamin D production

Biomimetic Artificial Kidney Device





Hemodialysis → Membrane filtration of albumin, urea and creatinine

Nutrients Reabsorption → Confluent renal tubule cell monolayer

Development of suitable membranes and coatings

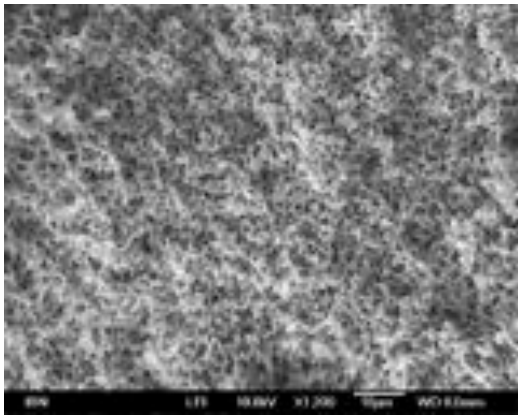
- Porous, non-fouling membrane
- Biocompatible membrane and suitable ECM coating to sustain the formation of differentiated epithelia with water channel expression

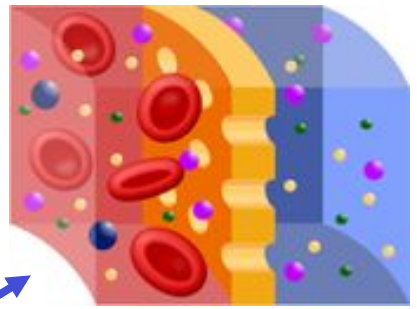
Hydrodynamic extrusion of membranes and cells as hollow fibers

Multi-Purpose Nanoporous Membranes

Water Purification

IBN's Membrane Technology





Hemodialysis, Kidney Assist Device

Sea Water Treatment

Waste Water Treatment

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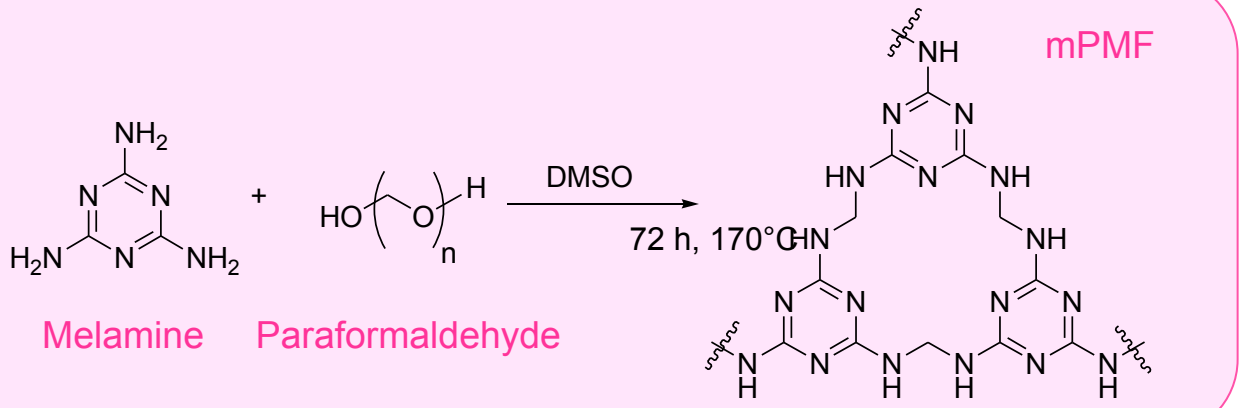
Capture and Storage of CO_2

- 30 wt% aqueous monoethanolamine for CO_2 capture
  – Requires heat treatment (> 100°C) to release chemisorbed CO_2
- Zeolites and MOF – Don't meet industrial requirements, expensive

Mesoporous Poly-Melamine-Formaldehyde (mPMF)

- Novel porous organic polymer (POP) with high surface area and porosity
- High density of functional groups
- Less basic amine (melamine pK_a 5.5) would favor CO_2 physisorption

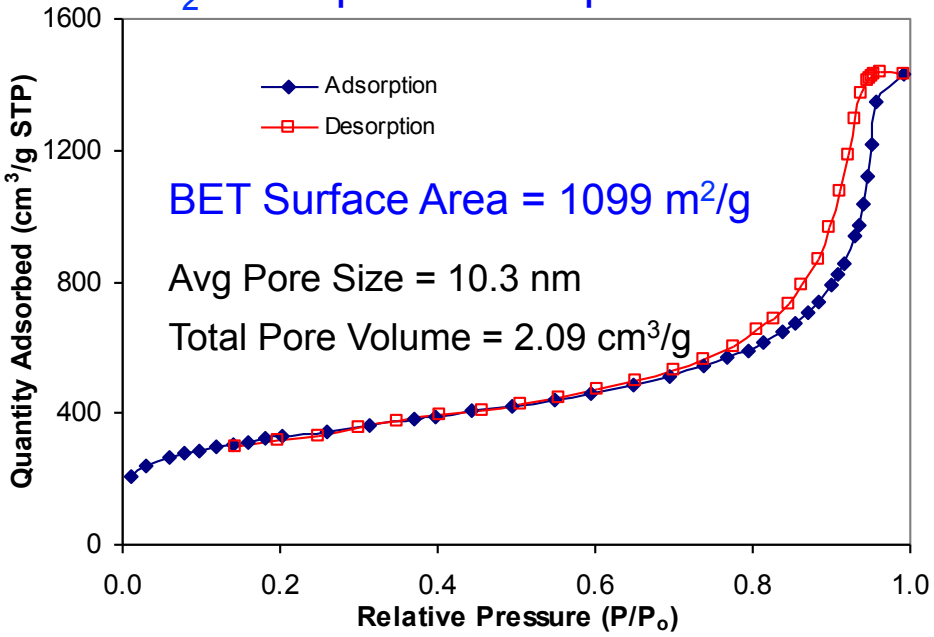


ChemSusChem (2013)

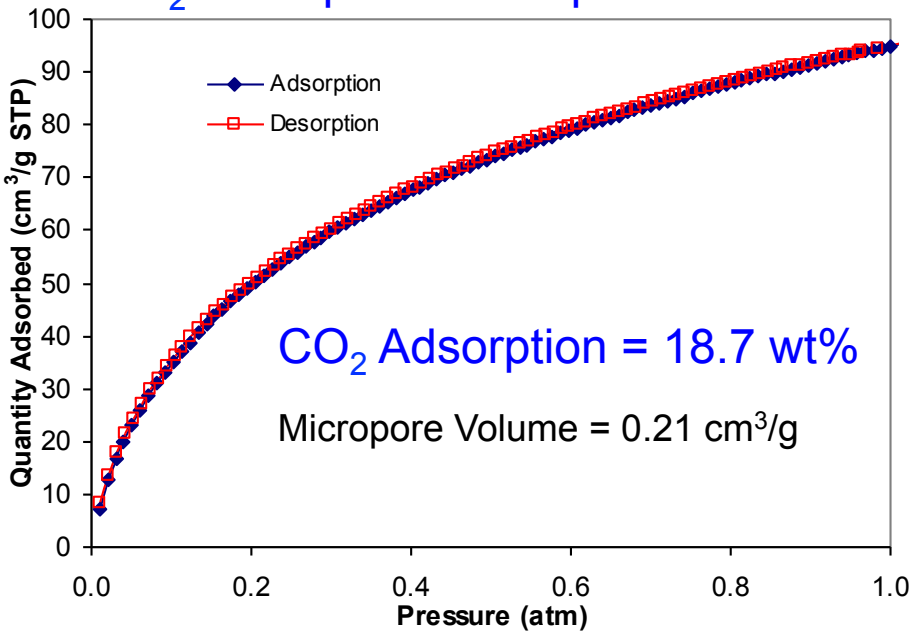
- Abundant and inexpensive starting materials
- Simple one-step synthesis, no templates or porogens

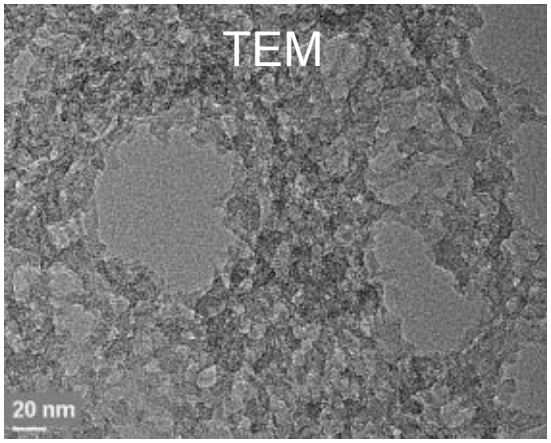
Characterization of Mesoporous PMF

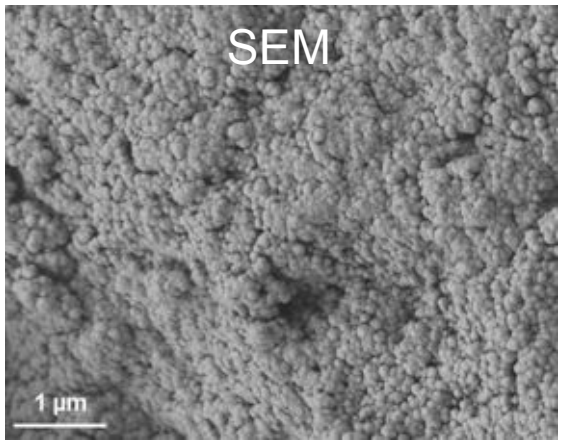
N_2 Adsorption-Desorption Isotherm



CO_2 Adsorption-Desorption Isotherm







- Foam-like structure with mesopores
- Aggregates of sub-µm spherical particles

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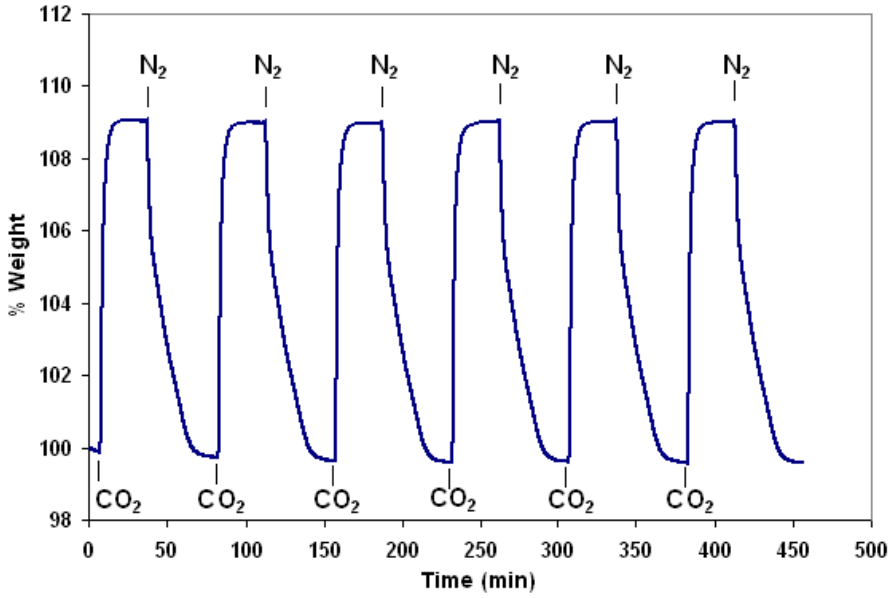
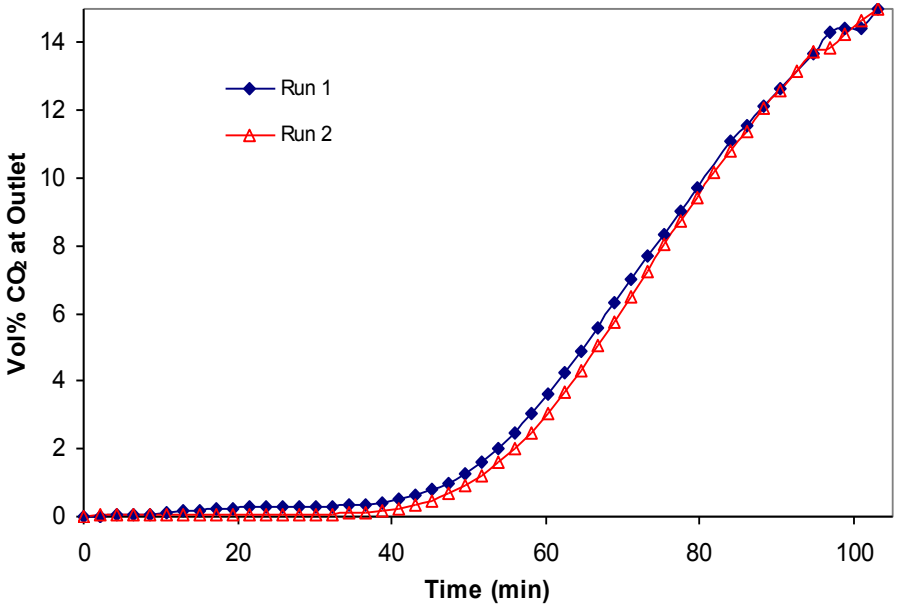
Reversible CO_2 Adsorption over mPMF





TGA Gas Cycling between pure CO_2 and pure N_2 at 25°C

- Instantaneous CO_2 adsorption at 20 ml/min
- Reversible, recyclable

Dynamic CO_2 Adsorption Analysis

- Gas flow rate: 2.5 ml/min; inlet: 15% CO_2 in N_2
- Total capacity of ~ 4.9 wt%
- Regeneration of mPMF via vacuum application

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Conversion of Greenhouse Gas

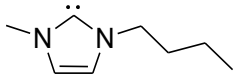
Problem – 5500 MT/year of carbon emissions causing global warming

Solution – Utilize CO_2 as a cheap, sustainable C1 feedstock

CO_2 —(Reductant)→ Methanol

Green Energy: Methanol (Market: 70 MT/year)

- Highly effective carbene organo nanocatalyst
  → Ambient reaction with > 90% yield



CO_2 —(R-C≡CH)→ R-C≡C-COOH R-C=C-COOH

Green Synthesis of Pharmaceuticals and Chemicals

- Propiolic acid, acrylic acid (US Market: 1.3 MT/year)

Impact – Novel catalysts and processes for licensing to green tech, chemicals and pharmaceuticals industries

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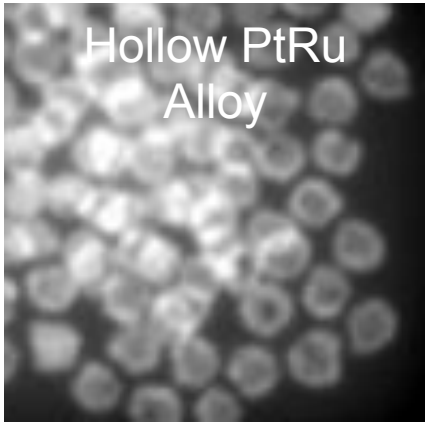
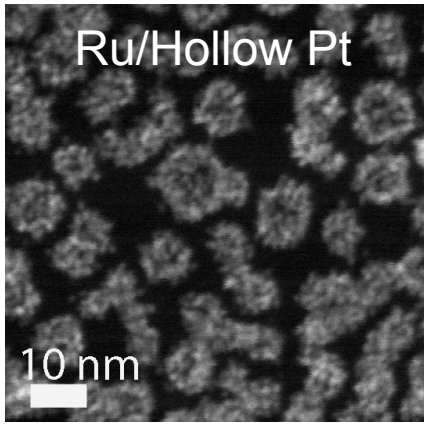
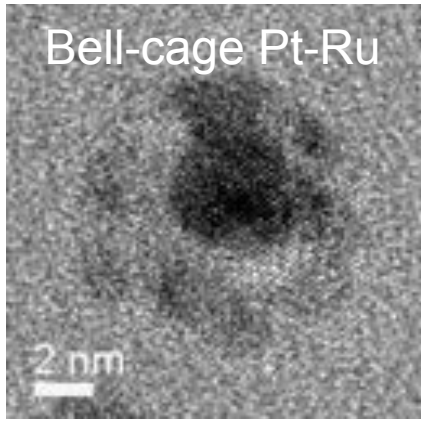
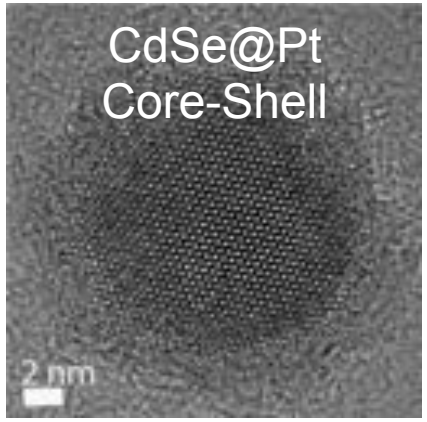
Advanced Materials for Energy Applications

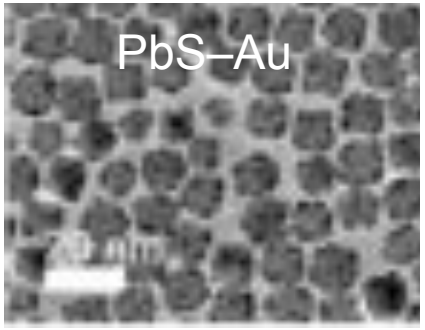


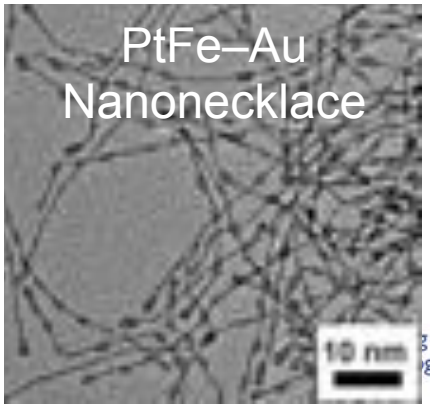






Nat. Mater. (2009), *J. Am. Chem. Soc.* (2010)





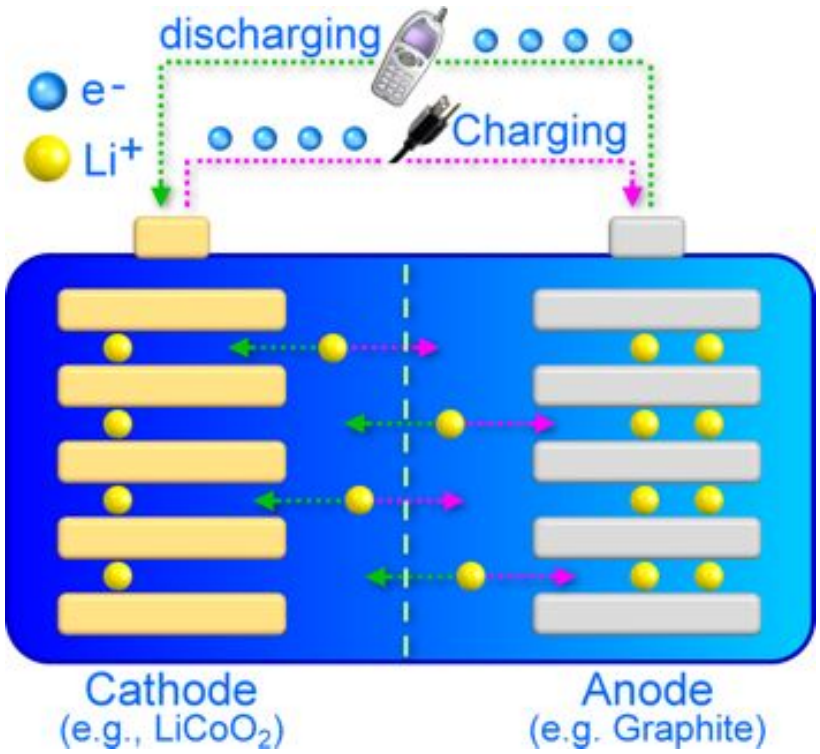
Nanocomposites of metals, semiconductors, oxides

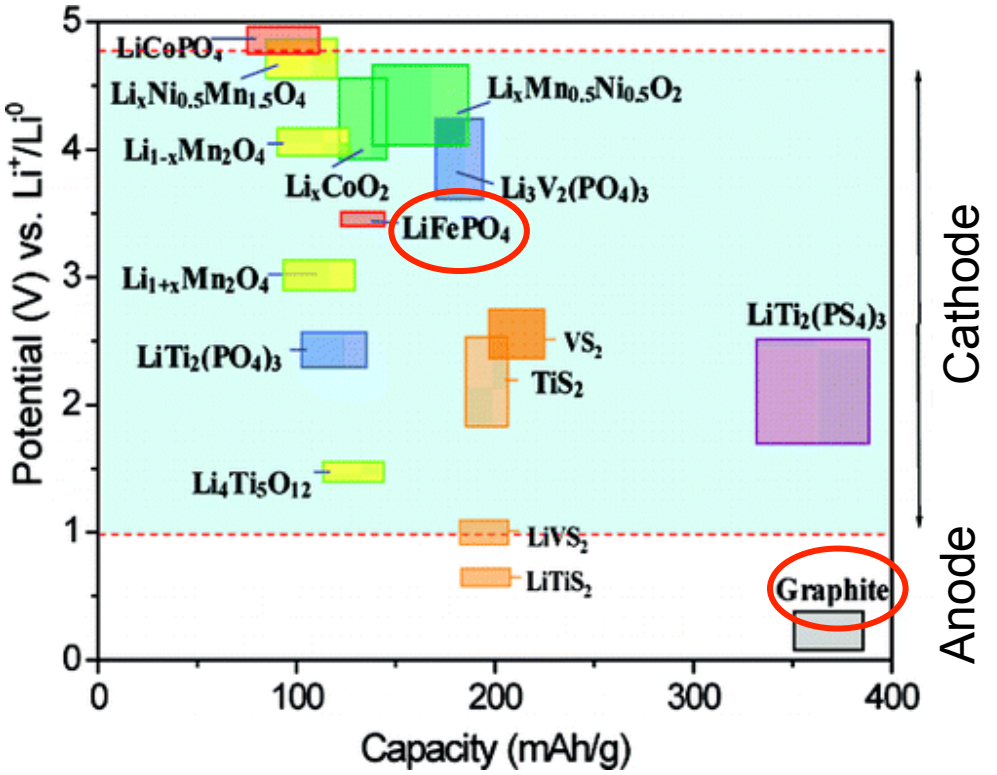
– Unique size effects and synergism between components
– Unprecedented control of microstructures, morphologies
→ Materials with superb activity, selectivity, efficiency

Clean, efficient conversion and storage of energy

- Fuel cells
- Solar cells
- Batteries

Electrodes in Lithium Ion Battery (LIB)





J. B. Goodenough, *Chem. Mater.* (2010)

- High power density (fast discharging rate), good cyclability
- High energy density (high capacity)
  - High operating voltage for cathode materials, e.g. $LiFePO_4$
  - Low operating voltage for anode materials, e.g. graphite

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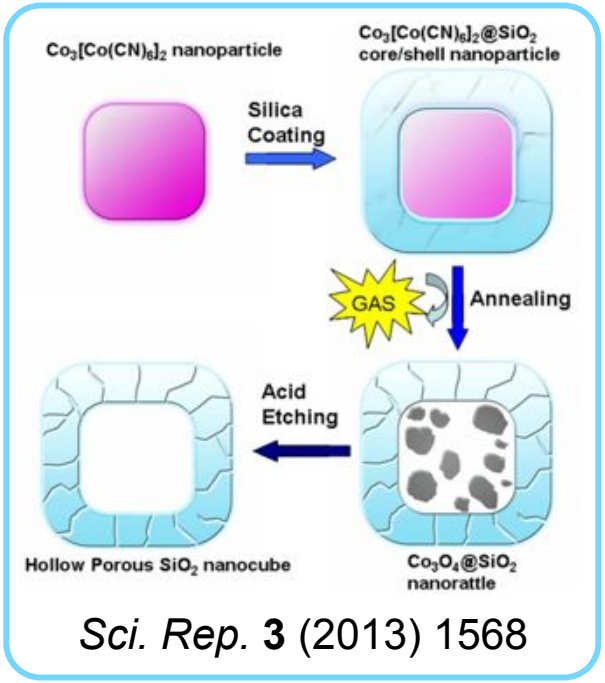
SiO_2 Nanocages for Li Ion Battery Applications

- Advantage of SiO_2 as a new anode material
  - High theoretical capacity (1965 mAh/g)
  - Inexpensive and abundant raw materials
- Disadvantage of recent synthesis method
  - Expensive $Co_3[Co(CN)_6]_2$ used as a template
  - $Co_3[Co(CN)_6]_2$ cannot be removed w/o annealing



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Our Approach

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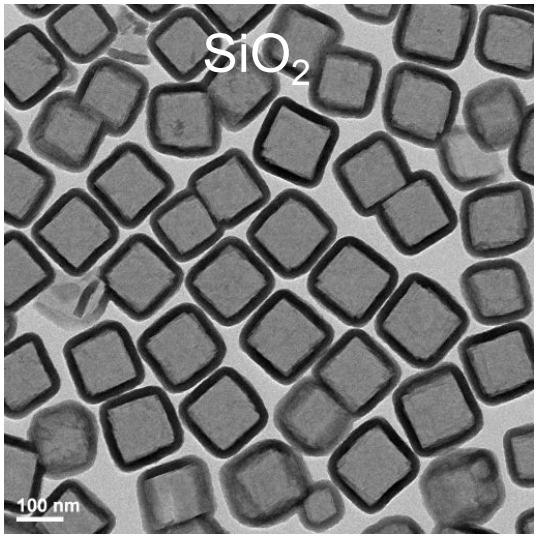
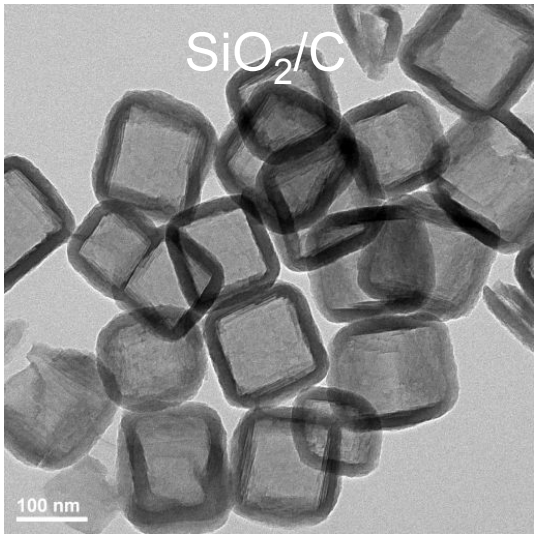
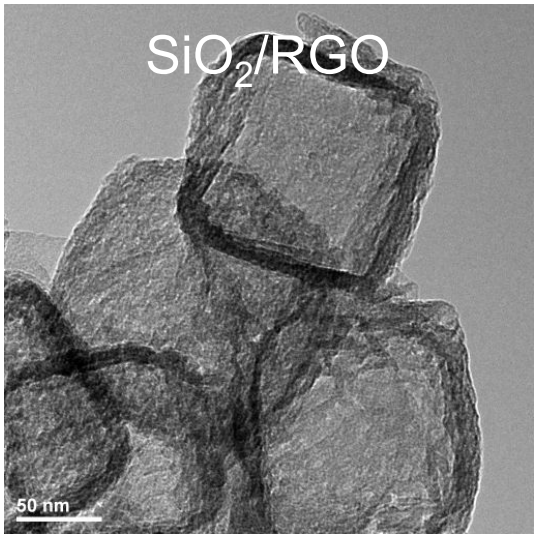
SiO_2 Nanoboxes with Carbon or RGO







SiO_2 nanoboxes + Lactose solution $\xrightarrow{\text{700ºC, Ar}}$ SiO_2/C

- No obvious morphological changed after carbon coating

SiO_2 nanoboxes + Graphene oxide $\xrightarrow[\text{180ºC, 12 h}]{\text{Hydrothermal}}$ SiO_2/RGO

- Highly porous wall of nanobox in SiO_2/RGO formed after hydrothermal treatment

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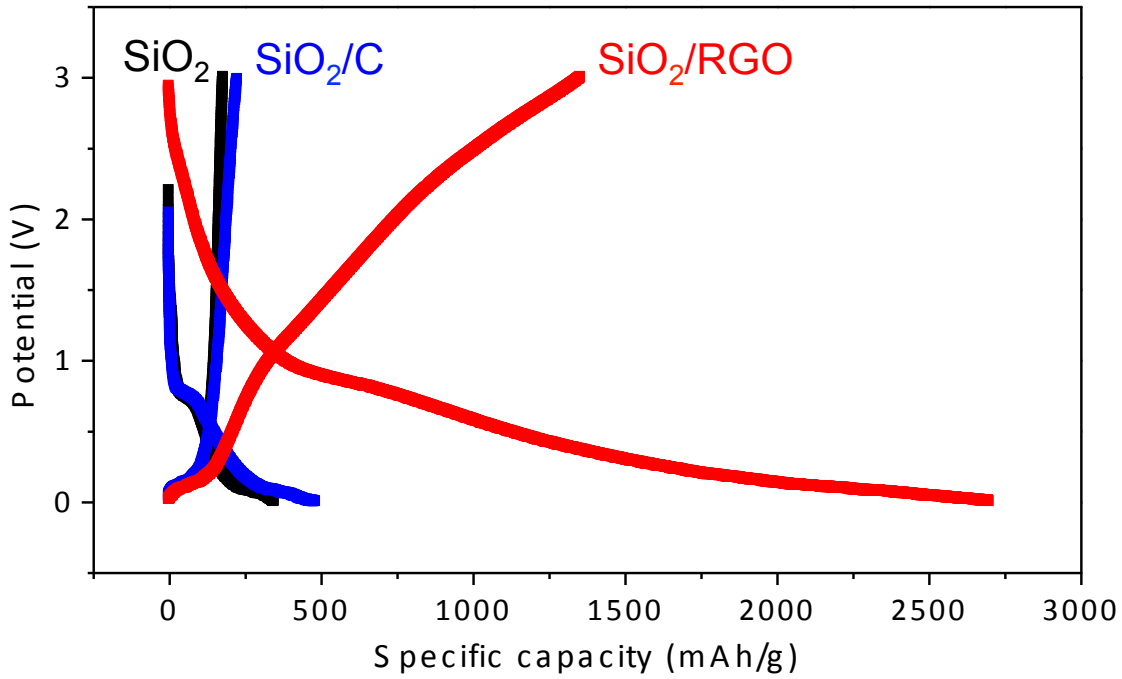
Battery Performance of SiO_2 Nanoboxes



	SiO_2	SiO_2/C	SiO_2/RGO
Discharging capacity (mAh/g)	345	480	2698
Charging capacity (mAh/g)	178	224	1353

- SiO_2/RGO nanocomposite has superb capacity

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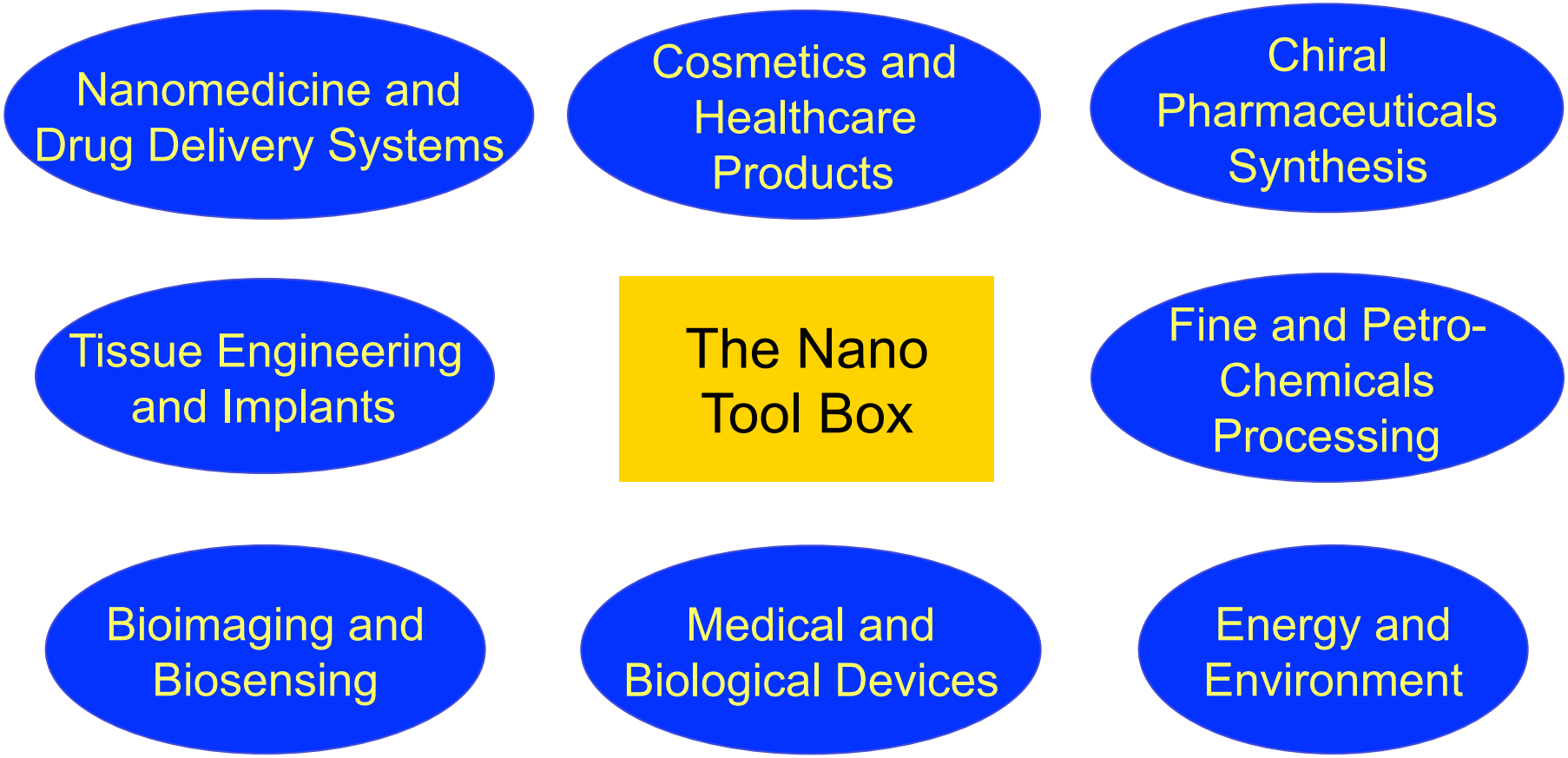
Applications of Nanostructured Materials/Devices



- Nanotechnology has been successfully developed as a tool box to engineer complex systems at multiple length scales with unique functionalities

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IBN's Youth Research Program (YRP)

- Launched in October 2003 to promote scientific research among the young
- Activities include open houses, career talks, science camps, workshops, research attachments for students and teachers
- To date, IBN has reached out to more than 76,200 students and teachers from 290 primary and secondary schools, junior colleges, polytechnics and universities
- IBN has trained over 2,000 full-time research attachments for ≥ 1 month period, including 155 scholars
- 51 YRP alumni have joined IBN as research staff

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