Application of bio-nanotechnology in Chinese medicines

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Nano biotechnology
- Nanoimaging
- Nanomanipulation
- Nanopatterning
- Nanoarray design and synthesis

Imaging-based Diagnostics
- Amyloid diseases
- Heart diseases
- Cancer

Nano-machines and sensors based on:
- Cantilevers
- Nano chips
- Smart materials to sense forces, fields and energies

On-demand, targeted delivery

Today Talk: Can Nanotechnology help Chinese Medicine get Global acceptance
Nanoscience and technology is about

- Understanding principles of physical world
- Designing Technology to unravel world

at the scale of molecules and structures that make and run the world we live in

Beginning of Nanotechnology and Nanomedicine

- Discovery of Nanotube
  - Nanoscale materials with magical properties for interactions with its environment
- Discovery of Scanning Tunneling and Atomic Force Microscopes (STM and AFM)
- Allow study of structures, motion and all physical forces at atomic scale in fluid
- Allow manipulating and creating structures at atomic scale
Accelerating Nanotechnology Applications to Human Health - Nanomedicine

- Global Population: >$10^{10}
- Human size: $10^0$
- Human cells: $10^{-6}$
- Biological macromolecules: $10^{-9}$
- Biological processes: $10^{-11}$-$10^1$
- Which means billions of us are controlled by structures and mechanics billionth times smaller (Nano) than us
  - Global Investment: >$10^{10}$
  - Current Global market: ~$10^{10}$
  - Global market by 2017: $10^{12}$
  - Global Nanobio companies: ~$10^3$
  - Disease Diagnosis: $10^1$
  - Disease Treatment: $10^1$
  - Disease Prevention: $10^1$

Can TCM gain a larger share of the market?
Define cause and Diagnose Pathology

Scope of Nano-biotech & Nanomedicine

Define Targets Receptors, Channels

Design Therapeutics Drugs, interventions

Targeted Delivery
- Controlled delivery,
- guided delivery
- On-demand release

Monitor Disease And Therapy states

Devices to Maintain Tissue Activity

Optimize Efficacy Minimize Side Effects

Devices for Tissue regeneration
- Stem cell therapy
- Wound healing
- Bone growth

In-vivo Sensors
- Diagnosis
- Remotely controlled
- Multi-functional

Diagnosis:
- high resolution and
- sensitivity

Therapy
- Reduce the Dose
- Treat localized cells/tissues
- Minimize side effects

- Biocompatible/non-toxic
- in Vivo Stability
- biodegradable
I will give examples of nanoimaging, nanomaterials and nanomechanics technology that relates to three essential components of all living systems (structure, motion and interaction with environment) can be used in Chinese medicine.

- Holistic Approach
- Medicine works by the synergistic action of many active constituents

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<th>Topics</th>
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**Nano-acupuncture**

**Delivering Chinese medicine to specific organs**

- Brain
- Lung
- Kidney
- Arm
- Leg

On-demand, targeted delivery

Data collected from Google Scholar
Nanoimaging for Nanomedicine

- Imaging functional ion channels
- Imaging amyloid (misfolded) channels
- Imaging single molecule proteolysis

Relevance to Heart and lung diseases, Alzheimer’s and other brain diseases, muscular diseases, cancer
Cell-Cell and Cell-Surround Communication Channels

A key Structure for the Evolution and Sustenance of Multicellular Organisms

Immunolabeling of hemichannel

Hemichannel

Gap

Cell 1

Cell 2

Closed

Open

Surface energetics map

3D topography

Extracellular

Cytoplasm

Smoking extract/ ROS Intake

Smoking induced lung diseases:

- Emphysema
- Cancer

Good and Bad of Amyloids

- **Amyloids as Foe**
  - Protein Misfolding → Amyloid Proteins → Accumulation as PLAQUES → Cell Death, Disease and System Failure

- **Amyloids as friend**
  - Infection → Amyloid Proteins (Anti-microbial Proteins) → Death of infecting agents

Is plaque, fiber or oligomer the mediator?
Amyloid peptides Induce dose-dependent synaptic degeneration

Jang et al, PNAS, 2010
Amyloid Diseases are a class of “Channelopathies” with Defined Ion Channels

Quist et al, PNAS, 2005
Real-time collagen-collagenase Association-dissociation

Defining Therapeutics’ Efficacy and Dosage

A key Extracellular matrix protein, provides support for tissue sustenance and growth

Single triple helical collagen I molecule: AFM image

Lin et al, Biochem, 1999
Nano-mechanics for Nanomedicine

• Sensing intermolecular interaction
• Sensing intracellular mechanics
• Sensing whole cell mechanics
• Sensing tissue mechanics
• Sensing composite materials mechanics
• In-vitro sensors for Biomarkers
• In-vivo Sensors for Biomarkers and therapy

Diagnostics, Designing therapeutics and Therapy monitoring
Single molecule spectroscopy on living cells

Locating Therapeutic Targets: VEGF Receptors

Integrated cantilever

AFM Tip

Cell membrane

Antibody

Antibody

Before adding VEGF

After adding VEGF

Online antibody addition

Probability

Unbinding force (pN)

0 min

10 min

45 min

0.00 0.01 0.02 0.03

0.00 0.01 0.02 0.03

0.00 0.01 0.02 0.03

68 ± 35 pN

78 ± 25 pN

110 ± 57 pN

163 ± 42 pN

Unbinding force (pN)

Probability

Unbinding force (pN)

Probability

Unbinding force (pN)

Probability

0 50 100 150 200 250 300

0 50 100 150 200 250 300

0 50 100 150 200 250 300

2 µm

25 µm

25 µm

25 µm

25 µm

200 kPa

100

50

0

200 kPa

150

100

50

0

Almqvist et al Biophys J, 2004
Nanomechanics of a Pulsating Muscle Cell

- Relevant to Muscular Disease Diagnostics and monitoring

Correlative Nano-Indentation and Tissue Elasticity with an AFM

Tissue stiffness-based diagnosis (cancer, MS, ALS, osteoporosis)

Understanding How Acupuncture works

Nano-acupuncture

Nano-electro-acupuncture

Parbhu et al, Biochemistry, 1999
Stickiness and Surface Roughness Of Composite Materials

Diagnostics for Infectious bacterial biofilm, sepsis, cell-substrate adhesion

Sherman, Quist, Hansma, J Nano Res, 2009
Patients with fractures: Indentation diagnosis


Kwok et al.
Nanomedicine: Nanotechnology, biology, Medicine, in press, 2014
Remote Sensor System for Various Organs/Tissues

Remote RF output signal from implanted edema sensor

Controller module for signal transmitter and signal receiver

RF, magnetic or thermal input signal and power

Computer analysis and control

Lung edema sensor

Brain edema sensor

Stent with attached sensor

Kidney edema sensor

Arm edema sensor

Leg edema sensor

Implanted edema sensor(s)

Lal, Raman, Jolly, Jin, US patent 2012
Remotely Guided in-vivo Theranostics

Nanodelivery for Diagnosis and Therapy

Remote electromagnet array

Motion in gradient field

Drug delivery capsule (MEMS or magnetically actuated)

Tumor or ulcer

Body cavity

Intestine wall

Magnetizable stripes

Swallowed camera

Modified from Raman et al, 2009
- Nanotubes
- Nanoclusters
- Nanoshells
- Dendrimers
- Nanoliposomes
  - Magnetically-vectored Nano-capsules
  - Nano bowls, nano-golf balls
Controlled and Targeted Theranostic NanoCapsules

Gate

Biocompatible Polymer

Targeting Molecule

On-off Gate

Under patent embargo
Magnetic Gold/Silica Nano Bowls and Capsules

For Targeting and controlled delivery

Silica Olive bowl Amine Functionalize Iron Oxide particles

Gold Seed Gold Plate Remove PS core

Moment (emu/g)

Magnetization (emu/g)

Applied Field (kOe)

Under patent embargo
Controlled Release using stimuli-sensitive Caps/coating

A: DNA closing
B: DNA motors opening and closing
C: encapsulation in hydrogel.

DNA based conjugation and actuation

Strand Displacement Devices

DNA thermal melting

Under patent embargo
Tight Junction

Blood

Endothelial cell array

Basement membrane

Brain

Switchable drug release from magnetic capsules

BBB crossing by gradient magnetic field

Blood

Endothelial cell array

Tight Junction

Drug capsule

BBB

Brain

Basement membrane

H (Step 1. BBB Crossing)

Switchable drug release on drug release

Permanent or electromagnet

N N N

S S S

For Brain Diagnosis and Therapy

Kong et al, J controlled Release, 2013
**Interdisciplinary Team**

- Nanobiophysicists
- Nanotechnologists
- Material Scientists/Engineers
- Biochemists
- Cell and system Biologists
- Medical Doctors

**Funding:**
- NIH
- NSF
- RC Nano Corp
- Alzheimer's Assoc
- Cal Dept of Health

**Group Members:**

**Research Scientists:**
- Srini Ramachandran M.D./ Ph.D.
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- Fernando Arce Ph.D.

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- Michael Hwang
- Joon Lee
- Nirav Patel
- Mukunth Vaidyanathan

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- Suri Sherman
- Celine Liong
- Max Yang
- Pavan Kanekal
- Sanam Mozaffari

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