Nanomedicine and the Road to Precision Medicine / Case Studies

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From Nanomedicine to Precision Medicine

“Personalized Nanomedicine”

- Pharmacogenomics (PGx)
- Pharmacokinetic (PK)
- Pharmacodynamic (PD)

Precision Medicine

Nanomedicine → Personalized medicine → Improved efficacy/safety → Approaching disease cure

Bio-imaging/bio-sensor
Targeted delivery
Enabling Technologies are essential for Better Life on Earth
Traditional Medicines:

Drug efficacy is questioned... [The right Drug and Dose/ for the Right Patient?]

Drugs 'don't work on many people'

A senior executive at Europe's largest drug maker has admitted most prescription medicines don't work for most people, it is reported.

Allen Roses, of GlaxoSmithKline, is quoted in a national newspaper as saying more than 90% of drugs only work in 30-50% of people.

He said: "Drugs on the market work, but they don't work in everybody."

Mr Roses, an expert in genetics, said new developments should help tailor drugs more specifically.

At present, pharmaceutical companies adopt a "one-drug-fits-all" policy.

But Mr Roses said refinements in genetic technology should make it possible to identify more precisely those people who were likely to benefit from a drug.
## Percentage of Non-responders

<table>
<thead>
<tr>
<th>Disease</th>
<th>Class</th>
<th>Percentage of Non-responders (%)</th>
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<tbody>
<tr>
<td>Asthma</td>
<td>β₂-Andrenergic Agents</td>
<td>40 – 75</td>
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<tr>
<td>Duodenal Ulcer</td>
<td>Proton Pump Inhibitors</td>
<td>20 - 70</td>
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<tr>
<td>Hyperlipidemia</td>
<td>HMG CoA Reductase Inhibitors</td>
<td>35 - 75</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Thiazide Diuretics</td>
<td>10 - 70</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Anti-Metabolite Therapy</td>
<td>20 - 50</td>
</tr>
</tbody>
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Source: B. Michael Silber, PhRMA R&D Directions Mtg., Feb. 2002
Traditional Medicines:
Drug safety is questioned... [Discontinue or Lower Dose?]

FDA Talk Paper

FDA Issues Public Health Advisory Recommending Limited Use of Cox-2 Inhibitors

Agency Requires Evaluation of Prevention Studies Involving Cox-2 Selective Agents

The Food and Drug Administration (FDA) today issued a Public Health Advisory summarizing the agency’s recent recommendations concerning the use of non-steroidal anti-inflammatory drug products (NSAIDs), including those known as COX-2 selective agents. The public health advisory is an interim measure, pending further review of data that continue to be collected.

In addition, FDA today announced that it is requiring evaluation of all prevention studies that involve the Cox-2 selective agents Celebrex (celecoxib) and Bextra (valdecoxib) to ensure that adequate precautions are implemented in the studies and that local Institutional Review Boards reevaluate them in light of the new evidence that these drugs may increase the risk of heart attack and stroke. A prevention trial is one in which healthy people are given medicine to prevent a disease or condition (such as colon polyps or Alzheimer’s disease).
The combined impacts of Nanotechnology will equal the Industrial Revolutions of the last two centuries — but with *all that change* compressed into *just a few years*
Top 5 Applications of Nanotechnology

- **1- Nanomedicine** (Drug Delivery Systems, Diseases Diagnostics, Screening, and Monitoring, Lab on a Chip, Tissue Engineering, Health Care Delivery,

- **2- Energy** Storage, Production, and Conversion,

- **3- Agriculture** Productivity/ Enhancement & Food Processing and Storage,

- **4- Water** Treatment, **Air** Pollution and Remediation

- **5- Supercomputing**

Plus several others such as Construction, Textile, and Equipment
Nano – From the Greek word for “dwarf” and means for $10^{-9}$, or one billionth. In this case it refers to $10^{-9}$ meters, or 1 nanometer (nm). 1 nm is about 3 atoms long.
Nanomedicine

- Nanomedicine is the medical applications of Nanotechnology.

- Nanomedicine ranges from the applications of Nanomaterials to Nanoelectronic biosensors, Molecular Nanotechnology in: Pharmaceuticals, Biopharmaceuticals, Nutraceuticals, Cosmetics, Diagnostics, and other future health care applications.
Nanomedicine – New Era in Personalized Medicine

**In Vitro**
- Diagnostics
- Biosensor, Biomarker

**In Vivo**
- Diagnostic Imaging

**NANOMEDICINE Applications**

**Nano-therapeutics**
- Drug/vaccine, peptide, gene delivery

Theranostics: ‘Image/Monitor and Treat’
Nanomedicine: Impact of Nanobiotechnology Toward Commercialization

Nanomedicine

Nanotechnology
Nano synthesis, Assembly, & Characterization
Nanoformulations Design

Biotechnology
Genomic & Proteomic
Molecular Medicine, Pharmacotherapy
Stem Cell

Applications
Early Detection Bioimaging, Biomarkers & Biosensors
Targeted Delivery Therapy Monitor

Commercialization
IP, Regulatory Affairs, Licensing, Scale up, Nano- Safety, and Clinical Development

PRI at Albany College of Pharmacy and Health Science
Nano Synthesis, Assembly and Characteristics
Nanoparticles: Multi-Functionality for Multiple Applications
Nanoparticles & Applications

**Drug Delivery**
- Small Molecules
- Peptides, Biologics

**Gene Therapy**
- Gene Up- or Down- Regulation

**Imaging**
- MRI, PET, Ultrasound, SPECT, CAT

**Implants**
- Sustained Release, Biocompatible NPs, Hydrogel

**Tissue Engineering**
- Bone Patch, Cardiac Patch, Vascular Patch
Nano Carriers and Medical Applications

- **Nanodiamons**
- **Carbon nanotubes**
- **Cyclodextrines**
- **Peptides**
- **Lipid nanoparticles**
- **Viral vectors**
- **Dendrimers**
Nanotechnology applications in Hematological Malignancies


ALCL = anaplastic large cell lymphoma
Case Studies

Nanomedicine and Drug Discovery and Development (Shorten time, Mitigate Risk, Extend Product Life Cycle)

I) Reformulation

II) Targeted Drug Delivery (Improve Efficacy and Safety)
   A- Oncology – Chemotherapy,
   B- Infectious Diseases – Anti-microbial and Anti-viral

III) Nanomedicine and Blood Brain Barrier - Glioblastoma
Drug Discovery and Development (DDD)

Could Enabling Technologies (Nanobiotechnology) Shorten Time to DDD and Mitigate the Risk?
Could Enabling Technologies (Nanobiotechnology) Accelerate and Improve DDD?

- **Existing Drugs:**
  1. Reformulation for Improved **PK** and **PD**:
     (oral heparin, oral Insulin, Combination of multiple RX).
  2. Targeted Delivery: **PK, PD, and Safety** (Chemotherapy, anti-Viral, anti--microbial)

- **New Drugs:**
  1. Formulation for Improved **PK and PD**
     (Certain Biologics, Antibody)
  2. Targeted Delivery
     (Genomic vs. Non-Genomic actions)
  3. Bioimaging (Early Detection/ Monitoring)
Robust, durable immunity by vaccination with single dose adjuvant-free HBsAg chitosan nanoparticle

Robust serum anti-HBs titers in mice immunized with nanoparticle-encapsulated HBsAg. BALB/c mice were immunized i.p. with a single injection of 1.5 µg of soluble free HBsAg (◆), nanoparticle-encapsulated HBsAg (■), or HBsAg alum (○). Weekly serum samples were analyzed for anti-HBs levels by ELISA. *p<0.05 2-way ANOVA.

Heparin Depolymerization Processes in LMWH Preparations

How is the endogenous heparin chain depolymerized?

ATIII = antithrombin III

Pentasaccharide is the smallest sequence that has affinity for ATIII
Clinical Trials with Oral Heparin Formulations: (PD-Anti-Xa) (Mousa et al., J Clin. Pharmacol 2007)

Results are presented as mean ± SD; n=8 per group

%F ~ 1%

TFPI (ng/mL)

Time (hours)
TEM image of Ag-DAPHP capped silver nanoparticles at (A) 160kx and (B) 340kx. (C) Particle size distribution (PSD) of Ag NPs is 7 nm ± 3 nm.

Nanoparticle interactions with the immune system

Nanoparticles can be engineered to either avoid interaction or to specifically interact with the immune system.

Immunostimulation
- Desirable
  - Vaccine efficacy
  - Antitumoral effects
- Undesirable
  - Hypersensitivity reactions
  - Inflammation
  - Anaphylaxis

Immunosuppression
- Desirable
  - Treatment of inflammatory disorders and autoimmune disease
  - Prevention of allergic responses
  - Transplant acceptance
- Undesirable
  - Lower body’s response to infected and cancerous cells
  - Myelosuppression and thymic suppression

Endocrinology 2010;151:458-465
## Re-formulation-Examples of Approved Drug Products with nm-sized API (nanocrystals and other Nanoformulations)

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Active Ingredient</th>
<th>Dosage Form</th>
<th>Sponsor</th>
<th>Nanotechnology Platform Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapamune</td>
<td>Sirolimus</td>
<td>Tablet (1 mg and 2 mg)</td>
<td>Wyeth</td>
<td>Ball Milling</td>
</tr>
<tr>
<td>Emend</td>
<td>Aprepitant</td>
<td>Capsule (40 mg and 125 mg)</td>
<td>Merck</td>
<td>Ball Milling</td>
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<tr>
<td>Tricor</td>
<td>Fenofibrate</td>
<td>Tablet (48 mg)</td>
<td>Abbott</td>
<td>Ball Milling</td>
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<tr>
<td>Triglide</td>
<td>Fenofibrate</td>
<td>Tablet (50 mg and 160 mg)</td>
<td>First Horizon</td>
<td>Microfluidizer</td>
</tr>
<tr>
<td>Megace ES</td>
<td>Megestrol</td>
<td>Oral suspension (125 mg/mL)</td>
<td>Par</td>
<td>Ball Milling</td>
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<tr>
<td>Invega Sustenna</td>
<td>Paliperidone Palmitate</td>
<td>Injectable suspension</td>
<td>Johnson &amp; Johnson</td>
<td>Ball Milling</td>
</tr>
<tr>
<td>Abraxane</td>
<td>Paclitaxel</td>
<td>Injectable suspension</td>
<td>Celgene</td>
<td>High Pressure Homogenizer</td>
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*J. Pharm. Sci., 102 (11), 3867 (2013)*
### Examples of Approved Liposome Formulations

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<th>Dosage Form</th>
<th>Sponsor</th>
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</thead>
<tbody>
<tr>
<td>Doxil</td>
<td>Doxorubicin Hydrochloride</td>
<td>Injection (20 mg/10 mL and 50 mg/25 mL)</td>
<td>Jansen</td>
</tr>
<tr>
<td>Abelcet</td>
<td>Amphotericin B Lipid Complex</td>
<td>Injection</td>
<td>Sigma Tau</td>
</tr>
<tr>
<td>Amphotec</td>
<td>Amphotericin B Lipid Complex</td>
<td>Injection (100 mg/vial and 50 mg/vial)</td>
<td>Alkopharma</td>
</tr>
<tr>
<td>DaunoXome</td>
<td>Daunorubicin Citrate</td>
<td>Injection (2 mg base/mL)</td>
<td>Galen</td>
</tr>
<tr>
<td>AmBisome</td>
<td>Amphotericin B</td>
<td>Injection (50 mg/vial)</td>
<td>Astellas</td>
</tr>
<tr>
<td>Depocyt</td>
<td>Cytarabine Lipid Complex</td>
<td>Injection (10 mg/mL)</td>
<td>Pacira</td>
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<tr>
<td>Visudyne</td>
<td>Verteporfin</td>
<td>Injection</td>
<td>QLT</td>
</tr>
<tr>
<td>Exparel</td>
<td>Bupivacaine</td>
<td>Injection</td>
<td>Pacira</td>
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*J. Pharm. Sci., 102 (11), 3867 (2013)*
Case Studies

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Active Targeting Modalities [Small Molecules, Antibody, Aptamer, and others]

Example

The αvβ3 integrin is generously expressed by tumor cells and rapidly-dividing blood vessel cells, enabling us to target these cell populations with Nano-Propyl Diamino tetrac.
Nano-Targeted (Nano-Diaminotetrac) Delivery of Chemotherapy (Cisplatin) into bladder cancer
DNA binders that induce cell death

Doxorubicin

Cisplatin
Tubulin inhibitors that prevent the cells from dividing

Vincristine

Taxol
Increased cisplatin uptake by bladder tumor by Nano-Diamino-tetrac targeted treatment


* \( P < 0.05 \) Vs. Cisplatin, ** \( P < 0.0001 \) Vs. Cisplatin or Nanocisplatin
Nano-Targeted (Nano-Diamino-tetrac) Delivery of Chemotherapy (Paclitaxel) into Pancreatic cancer
Paclitaxel uptake in pancreatic (SUIT-2) tumors

After 3 weeks of treatment with paclitaxel, Nano-paclitaxel or Nano-Diamino-tetrac-paclitaxel


**P <0.001 versus paclitaxel or Nanopaclitaxel**
Targeted Delivery of NPs- CD24 in orthotopic prostate Tumor
Targeting Resistant Prostate tumor and its Cancer Stem Cells

CD24 fluorophore signal (Cy7) in prostate tumors

Bioluminescent signal in prostate tumors


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Effect of Nano-Diaminotetrac, Thyroid-αvβ3 (Thyrointegrin) antagonist orthotopic Glioma (C6-luc) after 5 days of treatment

Similar Results were shown with U87 and other GBM cells Xenograft or Orthotopic
Nanomedicine and Future Advances

- Multi-functional Diagnostic Imaging: Matching a Tumor To a Drug (Personalize)
- Improve Efficacy and Safety of existing Drugs
- Targeting the Immune System at tumor/micro-environment
- Gene Therapy for Limited Gene Mutations (Rare Diseases)
- Biosensor and Auto-Medicine Delivery
- Biocompatible Implants and body parts (Tissue Regeneration)

“Increased Awareness, Increased Compliance, Improved Disease classifications, and Improved Quality of Life”
Virus Seeking Probes

Source: http://science.nasa.gov/headlines/y2002/15jan_nano.htm

Nano-Robots Replacing Neurons (Repair)


Why Nanomedicine?

- Nanotechnology offers great advancements to medicine
- There is still a lot to be learned about the human body and nanotechnology offers a lot of help.

Source: http://foresight.org/Nanomedicine/Gallery/index.html

Artery Cleaner

Source: http://foresight.org/Nanomedicine/Gallery/index.html
## Acknowledgements

**PRI, ACPHS**

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<tr>
<th>Name</th>
<th>Institution</th>
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<td>The Johns Hopkins University</td>
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