NANOMEDICINE: RECENT DEVELOPMENTS AND OPPORTUNITIES IN AFRICA

4th Biennial Conference

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Date: 9th October 2012
Introduction to nanomedicine
Recent developments in nanomedicine
Potential of nanomedicine in drug development
TB and Malaria as a case study
Our progress
Conclusion
INTRODUCTION TO NANOMEDICINE
**Nanotechnology:**
Manipulation of matter at atomic/molecular level

**Nanomedicine:**
Applications of nanotechnology in health: Mainly for treatment, diagnosis and monitoring of diseases
How small

Ant head - 1mm

Human hair - 100um, 100 000 nm

Red blood cell - 10um, 10 000 nm

NANOMEDICINE - 100 nm to 500 nm

0.1% of human hair width or

1% of smallest human cell

DNA - 4nm wide

Water molecule - 0.2 nm

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Nanocarriers are multifunctional, targeted devices, capable of crossing all biological barriers to deliver multiple therapeutic agents directly to diseased cells and disease-associated tissues.

- **Size**
  - Biological barriers
  - Increased cellular uptake
  - Versatile routes of admin
  - Solubility
  - Large surface area to volume ratio

- **Surface**
  - Large and active
  - Tailor ability
  - Targeted
    - Early detection
    - Imaging
    - Diagnosis
    - Treatment
    - Disease monitoring
  - Surface charge
Bioavailability problems and toxicity - a summary

- First-pass metabolism contributes to low oral bioavailability due to
  - GIT harsh environment
  - Poor permeability
  - Enzymes and transporters

- At intestine
  - Efflux: P-glycoprotein (Pgp) pumps drug back to intestinal lumen for elimination in faeces
  - Cytochrome P450 enzymes (CYPs) metabolise drug so that only a fraction reaches systemic circulation unchanged

- At liver
  - Pgp pumps drug into bile
  - CYPs further metabolise unchanged drug

RECENT DEVELOPMENTS
Plasma Levels: tremendous prolonged half-life

(Single Dose, 50 mg/m²)

Gabizon et al., Cancer Res. 1994
Clinical PK Comparison of Total Paclitaxel Study C008-0

Abraxane – nano formulated (dose-adjusted to 175 mg/m²)

Taxol – free drug (dose 175 mg/m²)
Nanoencapsulated Itraconazole for the treatment of lung fungus

(R Bentes – unpublished 2012, Unv. of Brazilia)

Improved Bioavailability, Reduced Toxicity

A; treated with ITZ – 1mg/animal Daily for 2 weeks

B; treated with ITZ-NANO - 100µg/animal every 3 days for 2 weeks
<table>
<thead>
<tr>
<th>Product</th>
<th>Company</th>
<th>Drug</th>
<th>Formulation</th>
<th>Route of administration</th>
<th>Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxil</td>
<td>Sequus Pharmaceutical</td>
<td>Doxorubicin</td>
<td>Liposome</td>
<td>Intravenous injection</td>
<td>Kaposi sarcoma in AIDS</td>
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<tr>
<td>Amphocil</td>
<td>Sequus Pharmaceutical</td>
<td>Amphotericin B</td>
<td>Lipoplex</td>
<td>IV infusion</td>
<td>Serious fungal infections</td>
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<td>Ambisome</td>
<td>NeXstar Pharmaceutical</td>
<td>Amphotericin B</td>
<td>Liposome</td>
<td>IV infusion</td>
<td>Serious fungal infections</td>
</tr>
<tr>
<td>DaunoXome</td>
<td>NeXstar Pharmaceutical (Boulder, Colorado)</td>
<td>Daunorubicin citrate</td>
<td>Liposome</td>
<td>IV</td>
<td>Kaposi sarcoma in AIDS</td>
</tr>
<tr>
<td>Abelcet</td>
<td>The Liposome Company (Princeton, New Jersey)</td>
<td>Amphotericin B</td>
<td>Lipid complex</td>
<td>IV infusion</td>
<td>Serious fungal infections</td>
</tr>
<tr>
<td>Rapamune</td>
<td>Wyeth/Elan (Madison, New Jersey)</td>
<td>Sirolimus</td>
<td>Nanocrystal particles</td>
<td>Oral</td>
<td>Immunosuppressant in kidney transplant patients</td>
</tr>
<tr>
<td>Emend</td>
<td>Merck/Elan (Whitehouse Station, New Jersey)</td>
<td>Aprepitant, MK869</td>
<td>Nanocrystal particles</td>
<td>Oral</td>
<td>For chemotherapy patient to delayed nausea and vomiting</td>
</tr>
<tr>
<td>TriCor</td>
<td>Abbott (Abbott Park, Illinois)</td>
<td>Fenofibrate</td>
<td>Nanocrystal particles</td>
<td>Oral (oOral)</td>
<td>Primary hypercholesterolemia, hypertriglyceridemia</td>
</tr>
<tr>
<td>Megace ES</td>
<td>PAR Pharmaceutical (WoodCliff Lake, New Jersey)</td>
<td>Megaestrol acetate</td>
<td>Nanocrystal particles</td>
<td>Oral</td>
<td>Treatment of anorexia, cachexia, or an unexplained significant weight loss in patients with a diagnosis of AIDS</td>
</tr>
<tr>
<td>Abraxane</td>
<td>American Biosciences (Blauvelt, New York)</td>
<td>Paclitaxel</td>
<td>Albumin-bound nanoparticles</td>
<td>IV injection</td>
<td>Metastatic breast cancer</td>
</tr>
<tr>
<td>Elestrin</td>
<td>BioSante (Lincolnshire, Illinois)</td>
<td>Estradiol</td>
<td>Calcium phosphate–based nanoparticles</td>
<td>Transdermal</td>
<td>Treatment of moderate-to-severe vasomotor symptoms (hot flashes) in menopausal women</td>
</tr>
</tbody>
</table>
POTENTIAL OF NANOMEDICINE IN DRUG DEVELOPMENT
Almost 50% of drugs with some at Phase III fail; this drives up costs. 

Possible reasons for failure:

- half-life
- toxicity
- dose
- solubility
- dose frequency
TB drug pipeline (TB global alliance)

Existing drugs redeveloped or repurposed for tuberculosis
- Rifapentine
- Linezolid
- Gatifloxacin
- Moxifloxacin

New drugs developed for tuberculosis
- SQ-109
- PNU-100480
- AZD-5847
- TMC-207
- OPC-67683
- PA-824

Compounds in clinical development for the treatment of active tuberculosis
www.thelancet.com Vol 375 June 12, 2010

Novartis cancer drug pipeline

PHASE I/II

- Midostaurin
  ASM
- Dovitinib
  Solid & Hemat. tumors
- RAF265
  Solid tumors
- Lucatumumab
  Hemat. tumors
- BEZ235
  Solid tumors
- BKM120
  Solid tumors
- LDE225
  Solid tumors
- Deferasirox
  NTD
- Deferasirox
  Hered. Hematochrom.
- Panobinostat
  Hemat. tumors
- Everolimus
  Gastric cancer, Lymphoma
- Deferasirox
  Acromegaly and Carcinoid
- Pasireotide
  GIST & cKIT Melanoma
- Panobinostat
  Multiple Myeloma
- Everolimus
  ER+ & HER2+ Breast Cancer

PHASE III

- INC424
  Myelofibrosis
- Panobinostat
  Hodgkin’s lymphoma
- Midostaurin
  AML
- Everolimus
  HCC
- Everolimus
  TSC AML
- Everolimus
  ER+ & HER2+ Breast Cancer

it’s been 40 years since the last new drug, yet only 2 drugs going through phase III clinical trials!
TB AND MALARIA AS A CASE STUDY
• TB leading cause of death in SA, highest infection rate in the world due to:
  • Co-infection of HIV and TB in 80% of cases
  • Patient non compliance; length of treatment (6-9 months)
  • Poor bioavailability and toxicity, hence:
    • Multi-drug resistant TB (MDR-TB) Extremely resistant TB (XDR-TB)
• **MDR TB 1-2 years treatment**
  - 50% die
  - 100X more expensive to treat
  - As infectious

• **Implementation of DOT’s program**
  - 53% cure rates; WHO target is 85%
  - Logistics are impractical
  - Expensive program, hospitalization
  - Education

• **Annual expenditure of TB drugs in SA**
  - Valued at 21.8M USD

• **SA annual TB treatment expenses (e.g. DOTS, hospitalisation)**
  - Estimated at 250-300M USD
Objectives

- Improve the bioavailability of anti-TB drugs
  - Nanocapsule: slow release
  - Minimise drug-drug interactions
  - Improve solubility and half-life
- Reduce dose
  - Size: improve biodistribution
- Reduce dose frequency
  - Polymer degradation: Sustained release over days
- Reduce treatment time and cost
  - 6-9 months: potentially 2 months
  - Current drugs cost: 1% of the total treatment management
OUR PROGRESS
• Successfully nano encapsulated 4 of first line anti-TB drugs
  – Using double emulsion solvent evaporation - spray drying technique
  – PCT patent application filed
• Properties:
  – 200 nm average size
  – Highly reproducible production
  – Scalable (known pharmaceutical process equipment)
  – Narrow size distribution (polydispersity < 0.1)
  – Controllable surface charge
  – Modified surface
    • Increase circulation time: PEG
    • Enhance particle uptake: Chitosan
• Developed other encapsulations systems
  – Natural polymers
  – Other synthetic polymers (Polycaprolactone)
  – Establishing a drug delivery platform
    • ARVs
    • Malaria and other PRDs
    • Other products like cosmetics, fertilizer and veterinary medicine
Where the TB nanomedicines go in the body:

- Lungs
- Liver
- Kidney
- Spleen
- Brain
- Heart muscles
Particles are mobile within the cell.
*In vivo* release, Swai *et al* unpublished data

- Increase in drug half-life
- PK of RIF and INH show slow release

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- Encapsulated INH/RIF administered once a week vs free RIF/INH administered daily
- Comparable reduction in lung lesions with reduced dose frequency
Efficacy of aptamer conjugated nanoparticles of Rifampicin

- *in vitro* superiority of targeted nanoparticles

![Bactec 460 readings of infected BM cells](image)
• Targeted drug delivery
  • Target either the liver or RBC stage of the parasite
  • Identify unique markers in parasite infected RBC or liver cells
    • Targeting ligands
    • Responsive polymers (micro environment changes)
    • Polymer conjugate
Nanomedicine for Malaria:

- Encapsulation of Malaria drugs
- Possible targeting approaches
Our achievements and impact so far

State of the art laboratories

Nanomedicine for TB project

Public engagement

- Pan-African Centre of Excellence in Nanomedicine

HCD:
- 20 international exchanges
- 7 Postdocs
- 4 PhD
- 6 MSc
- Over 15 BTech

International collaboration

Public engagement
Nanomedicine Workshop for Poverty Related Diseases: Nanomedicine Skills

- Opened by Minister of DST, HE Ms Naledi Pandor
- First Pan-African Nanomedicine Summer school Nov 2012

International Workshop on Nanomedicine for Infectious Diseases of Poverty, 27 – 31 March 2011
What is the future? MDRTB/HIV as an

14 tablets everyday for 2 years
ZAR 200 000 per patient

2 tablets once a week for 2 months
ZAR 2 000 per patient
Acknowledgement

• CSIR Conference organising committee
• DST for funding the project all the way
• CSIR for infrastructure and support
• National and International collaborators for the insight
Thank you
Targeting nanoencapsulated anti-TB drugs to sites of infection:

**Mycolic acid and aptamer ligands for drug targeting**

<table>
<thead>
<tr>
<th>More detail:</th>
<th>% cells with 1 NP</th>
<th>2-5 NP</th>
<th>6-9 NP</th>
<th>10+NP</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLGA/INH</td>
<td>12/20 = 60%</td>
<td>6/20 = 30%</td>
<td>0/20 = 0%</td>
<td>2/20 = 10%</td>
</tr>
<tr>
<td>PLGA/INH/MA</td>
<td>3/22 = 13.6%</td>
<td>11/22 = 50%</td>
<td>2/22 = 9.1%</td>
<td>6/22 = 27.3%</td>
</tr>
<tr>
<td>PLGA/RIF/Aptamer</td>
<td>7/35 = 20%</td>
<td>15/35 = 42.9%</td>
<td>4/35 = 11.4%</td>
<td>9/35 = 25.7%</td>
</tr>
</tbody>
</table>

![Graph showing % of NP containing cells](image-url)