Nanomedicine: An Innovative Approach Towards Treating Tuberculosis

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TB: Prevalence in South Africa

South Africa TB Statistics

- TB leading cause of death in SA
- Highest infection rate in Africa
- Fourth highest in the world

Due to:

- Co-infection of HIV and TB in 80% of cases
- Patients non compliance
  - Poor bioavailability
    - Treatment period (6-9 months)
    - Dose and dose frequency
    - Adverse side effect

- Hence
- Multi-drug resistant TB (MDR-TB)
- Extremely resistant TB (XDR-TB)
Conventional Oral Delivery System

Limiting factors for oral delivery

- **Gastric Intestinal Track (GIT):**
  - Harsh environment
  - Bioactives degradation
  - Poor permeability
  - Relatively short gastric emptying and intestinal transit time
  - Pre-systemic clearance

- **Hence:**
  - Poor bioavailability
    - Increased dose & dose frequency
    - Increased length of treatment
  - Drug toxicity
  - Drug-drug interaction
Nano encapsulated TB drugs

INH-loaded PLGA nanoparticles

CLSM image of macrophage cell taken up 1 um size particles

200 nm
Anti-TB drugs
Polymeric shell
Nanodrug delivery system in the GIT

Structure of the GIT

- Para-cellular via M cell
- Intracellular via epithelial cell-intestine mucosa
- Peyer's patches

Internal structure of the intestine

[Diagram showing the internal structure of the intestine with labels for Duodenum, Ileum, Capillaries, Endothelium, Basement membrane, Intima, Media, Adventitia, Smooth muscle cells, and Elastic fibres.]
Routes and mechanisms of particle transport across epithelia

- Modified surface
  - Increase circulation time: PEG
  - Enhance particle uptake: Chitosan
Promises of Nano-drug delivery

• Enhance anti-TB drug properties
  • Solubility
  • Rate of dissolution: sustained and controlled release systems
  • Oral bioavailability: minimise first pass metabolism
  • Targeting ability

• Enhance anti-TB drug dosing requirements
  • Reduced dose and dose frequency
  • Minimal adverse side effects
  • Shortened treatment time
  • Improve patient compliance

• Generic (platform) technology
  • Anti-malarials
  • ARVs
  • Anti-cancer drugs
  • Long term pain killers
  • Traditional medicines
Objectives

- Improve the bioavailability of ATDs
  - Minimise degradation of the drugs in the stomach
  - Steady and controlled release

![Graph showing concentration over time with controlled release and conventional therapy]

- Reduce the dosage and dose frequency
  - Treatment 4 drugs/day – 4 drugs/weeks
  - Improve patient compliance
  - Minimise the toxicity of drugs
  - Reduce the cost of TB treatment

- Targeting TB in infected macrophages
Proposed Solution

• Encapsulation of ATDs into multifunctional polymeric nanoparticles.
Project technical status

• 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
    • Other PRD’s
Encapsulation of all four drugs

- Encapsulation of pre-formed drug-loaded micelle-like containers
In vitro uptake in CaCo-2 cells

Z-stack 30 min incubation

60 min incubation

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In vitro uptake in THP-1 cells

a) Coumarin labelled
b) INH-PLGA
c) Rhodamine labelled
Tissue distribution of Rhodamine labelled PLGA nanoparticles after 1 day exposure (CLSM images)
Tissue sections: High dose of PLGA particles

- **LUNG**
- **KIDNEY**
- **LIVER**
- **SPLEEN**
- **BRAIN**
- **HEART MUSCLES**

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Release profile for free drugs vs encapsulated drugs: Improved formulation (Swai et al. unpublished data)

IN VIVO release

INH -2
INH-1
INH multi-drugs
Conv-INH
MIC-INH
RIF1
RIF2
Conv Rif
MIC-RIF
RIF Multidose
PZA1
PZA2
Conv-PZA
PZA Multidose
MIC-PZA
Progress summary

- Encapsulated 4 first line ATDs
  - PCT patent filed - double emulsion SD technique
  - Micelles
  - Natural Polymers
  - 2 further invention disclosures

- In vitro assays
  - In vitro efficacy
  - In vitro stability and slow release profile
  - Particle uptake

- In vivo assays
  - Macrophage uptake
  - No abnormalities in tissues
  - No inflammatory response
  - Sustained release profile over 6 days

- Generic technology
  - Anti-retrovirals, antibiotics etc.
  - In search of collaborators in Malaria and traditional actives
Active targeted drug delivery

- Inherent macrophage mechanisms being manipulated
  - Phagocytosis and endocytosis
  - Over expression of protein in TB infected macrophages
    - Direct mannose receptor mediated particle uptake
      - Novel technology
      - Aptamers against target protein
      - Preferential localization of particles
        - Macrophage over expressing protein

- Mycolic acid
  - Cell wall of *M. tb*
  - Directing nanoparticles to *M. tb* in cells

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Overview of drug delivery platform relationships & agreements

Legend:
- Core TB project
- TB targeting
- New Technologies R&D
Progress on HR Capacity Building

- **Recruitment progress**
  - 4 Post docs - Boitumelo Semete, Paul Chelule and Malebogo Legodi, Lebogang Katata
  - 4 PhD students – Yolandy Benadie, Lonji Kalombo, Lindiwe Nkabinde and Laetitia Booysen
  - 3 MSc students – Phumzile Hadebe, Saloshnee Naidoo and Trudy Maluleke
  - 4 Technikon students - Sonia Mathopo, Batabile Ramalapa and Koketso Rapatla and Mofahloshi Chuene

- **Training completed (2006-2008)**
  - University of London, UK
  - EPFL, Switzerland
  - PGIMER, Chandigarh, India.
  - University of Nottingham, UK
  - University of Cardiff, UK
  - University of Liverpool, UK

- **Training arranged for 2009 onwards**
  - National Jewish Medical and Research Centre, USA
  - University of Nottingham, UK
  - University of London, UK
  - University of Colorado, USA
THANK YOU