Nanomedicine for Improved Efficacy of Tuberculosis Drugs – Pharmacokinetic importance

Emerging Researcher Symposium

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Outline

• Challenges in TB treatment

• Nanomedicine as proposed solution

• Results

• Conclusions
Challenges for TB therapy

- One-third infected worldwide with 1.4 M deaths in 2010
- TB is a leading killer in SA
- Worsening due to Treat. failure & HIV co-infection
- South Africa is among the high burden TB and MDR-TB countries worldwide
- Lengthy treatment (6-9 months)
- Daily handful dose
- Patient non-compliance

14 Tablets everyday for 2 years
TB burden in South Africa

- South Africa accounted for 25% new and relapse cases of TB in Africa in 2010
- TB incidence rates stable/falling in all high incidence countries except in South Africa
TB drug pipeline not promising

- 90% chance of rejection in early-stage phase I clinical trials; 50% chance in phase II;
- Phase III drugs in TB pipeline can only replace 1 or 2 of the current drugs

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<tr>
<th>Regimen Development</th>
<th>Clinical Phase II</th>
<th>Clinical Phase III</th>
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<td>Moxifloxacin (+ H, R, Z) Bayer Enrollment completed</td>
<td>Moxifloxacin (+ R, Z, E) Bayer Enrollment completed</td>
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Novartis cancer drug pipeline

- http://www.novartisoncology.com/research-innovation/pipeline.jsp

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**Clinical Development**
- Clinical Phase I

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**New Drugs**
- TMC207/PA-824/Pyrazinamide
- PA-824/Pyrazinamide/Moxifloxacin

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**Novel Regimens**
- TMC207/Pyrazinamide
- PA-824/Pyrazinamide

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**Regimen Building Blocks**
- TMC207/PA-824/Pyrazinamide
- PA-824/Pyrazinamide

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Proposed solution to the challenges of TB treatment

• More efficient drugs and drug delivery system with improved pharmacokinetics →
  • Address non compliance,
  • Minimise toxicity,
  • Reduce emergence of drug resistance
  • Shorten treatment time

• Nanoparticle based drug delivery system (nanomedicine)
Pharmacokinetics (PK)

- Pharmacokinetics is the quantification of absorption, distribution, metabolism and excretion (ADME)
- Dictates availability of drug molecule at site of action
Nanomedicine

- Application of nanotechnology in health
- Nanosized drug delivery systems for treatment

Journal of Leukocyte Biology Volume 78, September 2005
Kinetics of nanoparticles influenced by...

- Size
  - Higher drug loading
  - Solubility
  - Large surface area
  - Allows intracellular uptake
  - nm size range particles more efficiently taken up than microparticles

- Charge
  - Surface charge influences plasma protein binding and cellular uptake

- Surface chemistry
  - PEG on surface increases blood circulation time
Pharmacokinetic advantages of nanomedicine

- Enhanced drug stability
- High carrying capacity
- Hydrophilic/hydrophobic substances
- Enhance absorption and bioavailability
- Reduce clearance
  - Minimised first pass metabolism
  - Increase in drug half life → prolonged effect
- Through slow release can reduce dosage and dose frequency
- Selective uptake by tissues (passive targeting)
- Delivery through lymphatic system
- Target specific tissue and cells (active targeting)

Conventional drugs

Nano-based drugs
Objectives

- Improve the PK of anti-TB drugs
  - Sustained release
  - Improve solubility and half-life
- Reduce dose frequency
  - Polymer degradation: Sustained release over days
- Reduce dose
  - Deliver drug at site of action
- Reduce treatment time and cost
  - 6-9 months: potentially 2 months
  - Current drugs cost: 1% of the total treatment management
Nanoparticles encapsulating anti-TB drugs (Nanodrug)

- Successfully nano encapsulated 4 of the first line anti-TB drugs
  - Isoniazid (INH), Rifampicin (RIF), Pyrazinamide (PZA) and Ethambutol (ETB)
  - Poly (lactide-co-glycolide) (PLGA) polymer
  - Double emulsion solvent evaporation - spray drying technique

- Properties:
  - 250 nm average size
  - Highly reproducible production
  - Scalable (known pharmaceutical process equipment)
  - Narrow size distribution (polydispersity < 0.1-0.3)
  - Controllable surface charge
  - Modified surface
    - Increase circulation time: PEG
    - Enhance particle uptake: Chitosan
Plasma circulation and biodistribution

Biodistribution of Rhodamine labelled PLGA nanoparticles coated with 1% PEG or Pluronics F127. 7 days after oral administration.
Pharmacokinetics in unchallenged mice

- Sustained release of RIF and INH from PLGA nanoparticles
- Increase in drug half-life
- Potential for dose frequency reduction
How does altered PK affect efficacy?

Female C57Bl/6 mice models of TB H37Rv at 50-100 cfu/lung

- Aerosol infection
- Confirmation of infection dose
- Determination of established burden
  - INH/RIF/PZA daily
  - Nano-INH/RIF/PZA once a week
  - Nanoparticles only
  - Untreated

Day 0

Day 1

W3

W7, W9, W12

INH = 5 mg/kg
RIF = 10 mg/kg
PZA = 20 mg/kg

- Data analysis
  - Bodyweight (weekly)
  - Lung weight
  - Pulmonary bacilli burden
  - Splenic bacilli burden
  - Pulmonary pathology

1 x 10^5 – 1 x 10^6 cfu/lung
3 x 10^3 cfu/spleen
Effects of the Nanodrug on *Mycobacterium tuberculosis* replication

- Nanodrug once a week vs conventional drug daily
- Treatment with nanoencapsulated TB drugs once a week, comparable to daily treatment with conventional drugs
Pulmonary pathology

- Untreated control
- Nanoparticle control
- RIF/INH/PZA daily
- Nano RIF/INH/PZA once a week
Increased circulation and slow release

Biodistribution of Rhodamine labelled PLGA nanoparticles coated with 1% PEG or Pluronics F127. 7 days after oral administration.

Slow release leading to increase in half-life
Conclusion

- Nanoencapsulated anti-TB drugs as effective as conventional drugs at fraction of dose

- Implications of nanomedicine to improve TB drugs,
  - Reduction in the dose frequency,
  - Promoting patient compliance to treatment
  - Targeting next step to reduce dose

- Generic technology
  - Can be applied to malaria, HIV and other poverty related diseases affecting Africa
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Thank you