Nanomedicine for Improved Efficacy of Tuberculosis Drugs – Pharmacokinetic importance

Emerging Researcher Symposium

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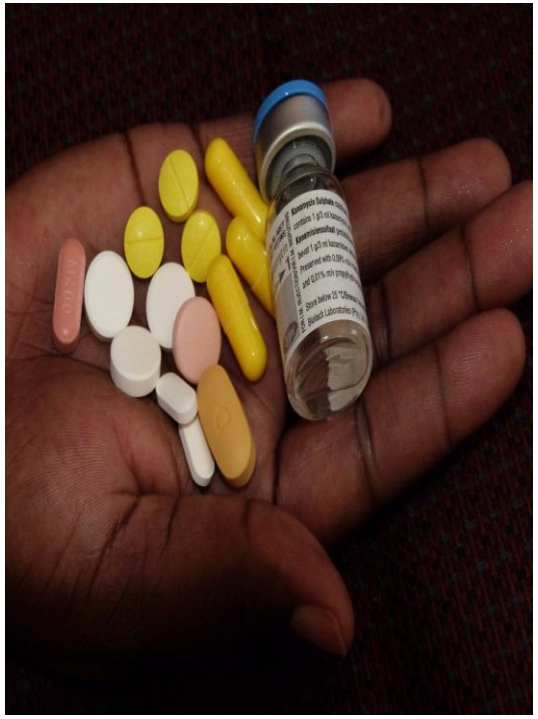
our future through science

Outline

- Challenges in TB treatment
- Nanomedicine as proposed solution
- Results
- Conclusions

Challenges for TB therapy

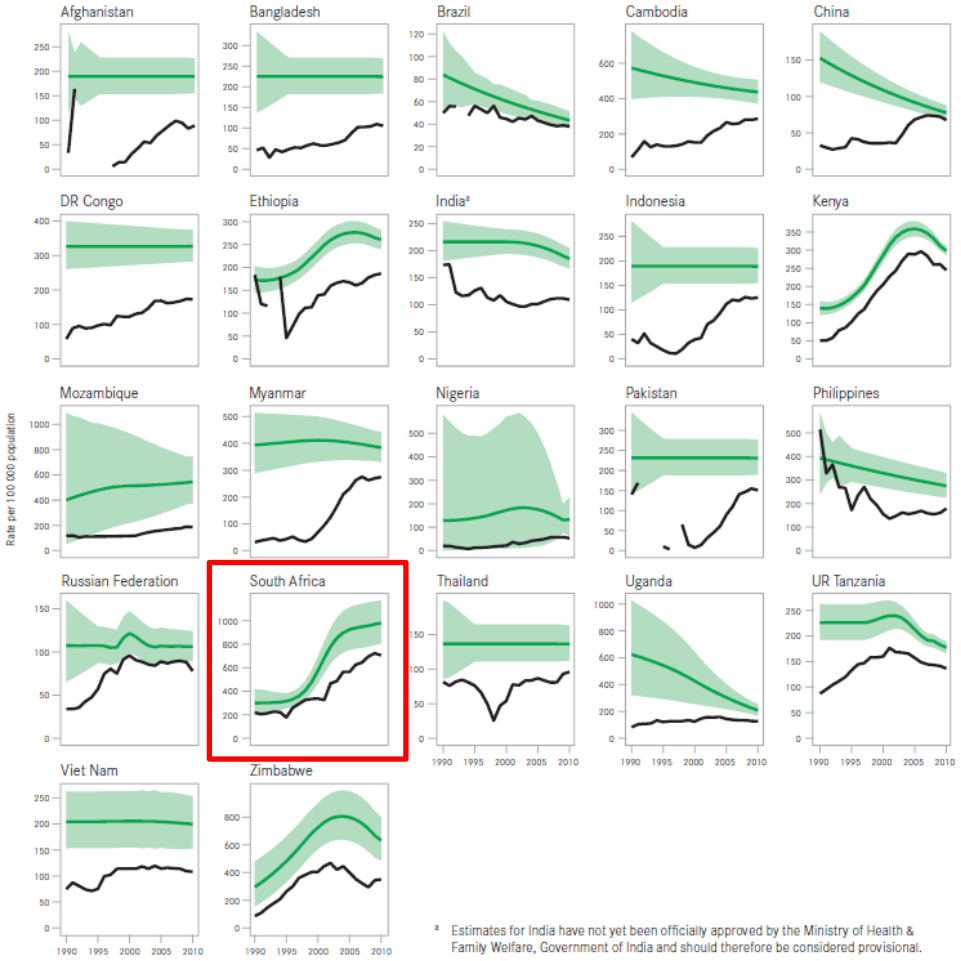
- One-third infected worldwide with 1.4 M deaths in 2010
- TB is a leading killer in SA
- Worsening due to Treat. failure & HIV co-infection
- South Africa is among the high burden TB and MDR-TB countries worldwide
- Lengthy treatment (6-9 months)
- Daily handful dose
- Patient non-compliance



14 Tablets everyday for 2 years

TB burden in South Africa

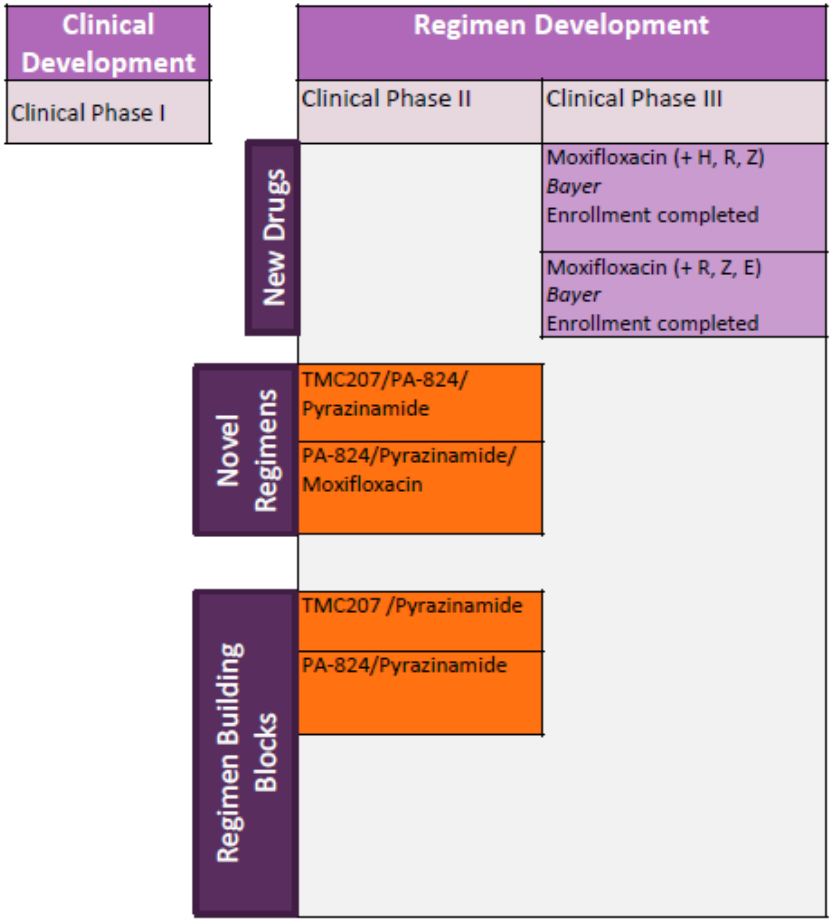
- South Africa accounted for 25% new and relapse cases of TB in Africa in 2010
- TB incidence rates stable/falling in all high incidence countries except in South Africa



[a] Estimates for India have not yet been officially approved by the Ministry of Health & Family Welfare, Government of India and should therefore be considered provisional.

TB drug pipeline not promising

TB drug pipeline (TB global alliance)



http://www.tballiance.org/pipeline/pipeline.php

Novartis cancer drug pipeline

PHASE I/II	PHASE III or PIVOTAL
LGX818 Solid tumors	Midostaurin[h] ASM[1]
RAF265 Solid tumors	Everolimus HCC[2]
BEZ235 Solid tumors	Everolimus HER2+ Breast Cancer
BKM120 Solid tumors	Everolimus Lymphoma
AUY922 Solid tumors	INC424[e] Polycythemia Vera*
LCI699 Solid tumors	Pasireotide[f] Acromegaly
MEK162[b] Solid tumors	Pasireotide[f] Carcinoid
LDE225 Solid tumors	Midostaurin[h] AML[3]
Panobinostat[c] Hemat. tumors	Panobinostat[c] Multiple Myeloma
Nilotinib cKIT Melanoma	Dovitinib[d] mRCC[4]
Everolimus Solid tumors	LDE225 Basal Cell Carcinoma
Dovitinib[d] Solid & Hemat. tumors	New molecule New indication

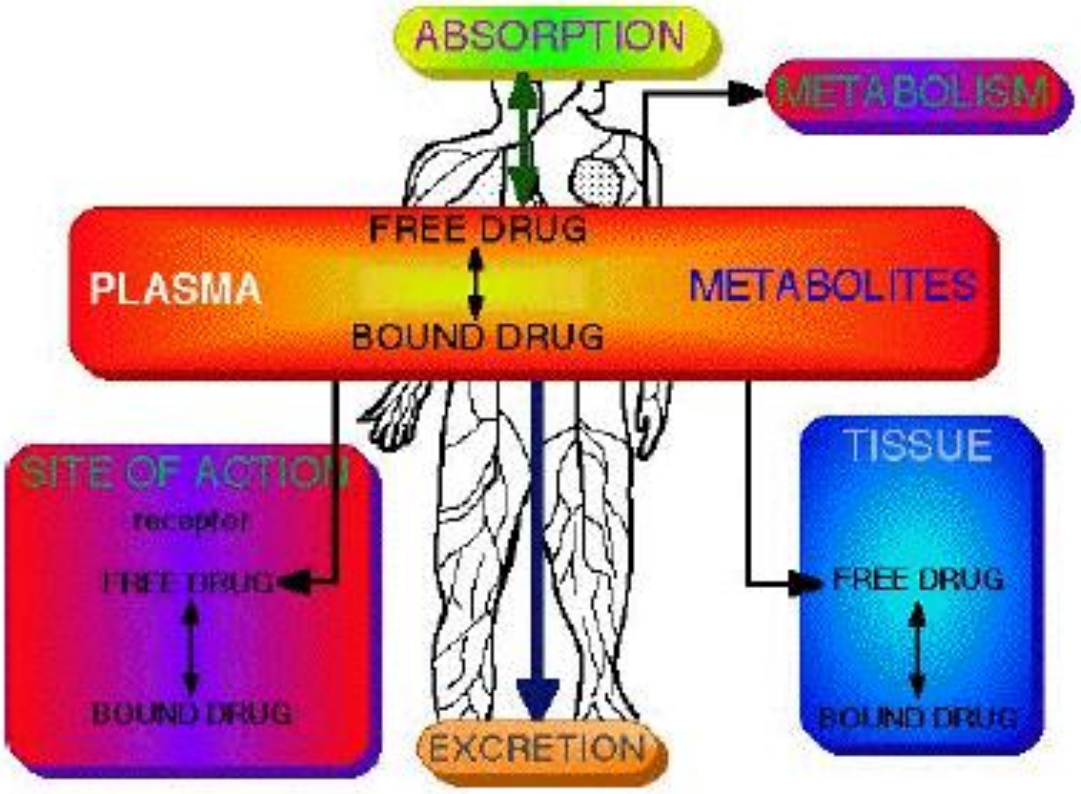
http://www.novartisoncology.com/research-innovation/pipeline.jsp

- 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

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)

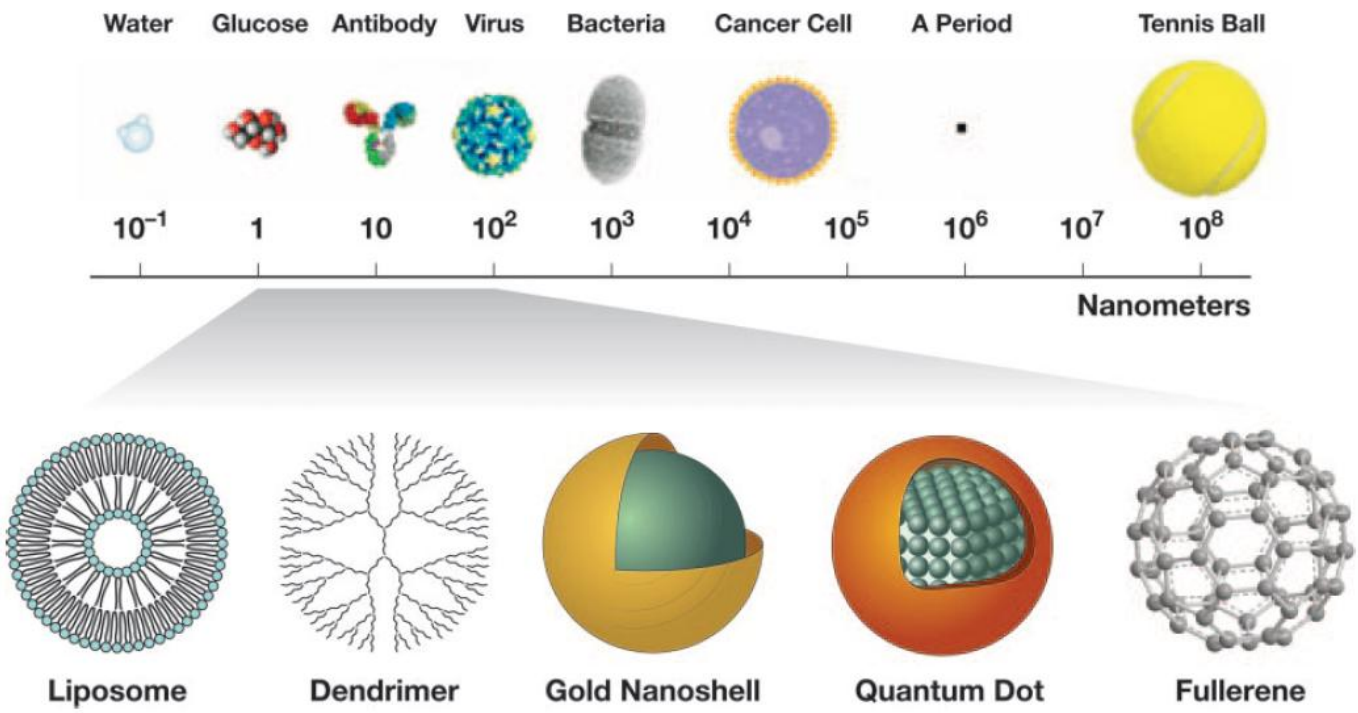
Pharmacokinetics (PK)



- 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



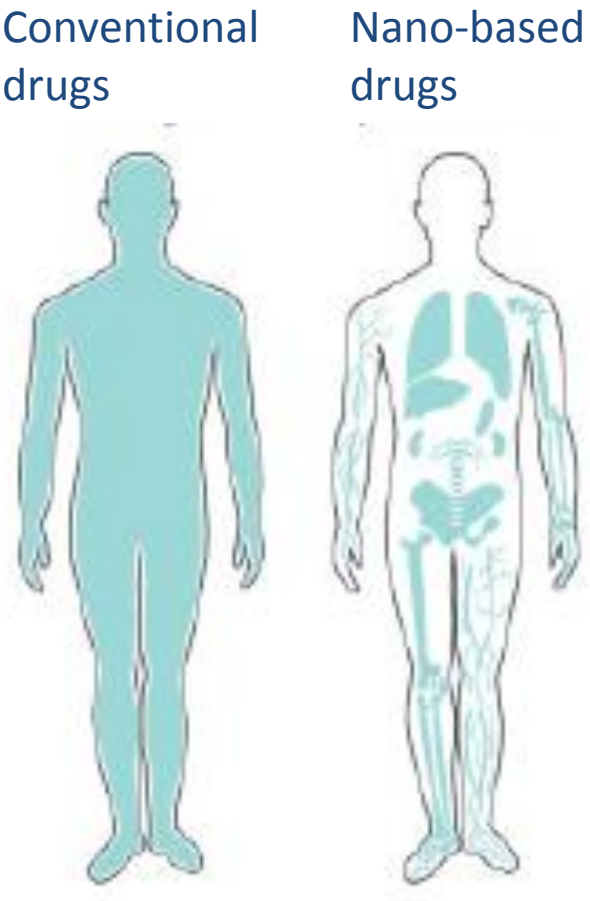
Journal of Leukocyte Biology Volume 78, September 2005

Kinetics of nanoparticles influenced by…

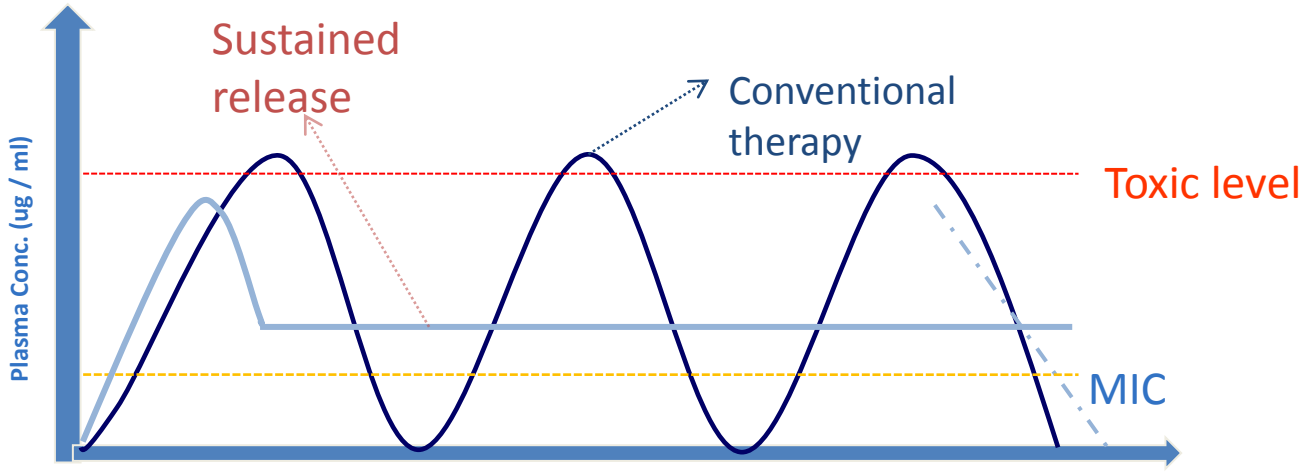
- Size
  - Higher drug loading
  - Solubility
  - Large surface area
  - Allows intracellular uptake
  - nm size range particles more efficiently taken up than microparticles
- Charge
  - Surface charge influences plasma protein binding and cellular uptake
- Surface chemistry
  - PEG on surface increases 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)



Objectives

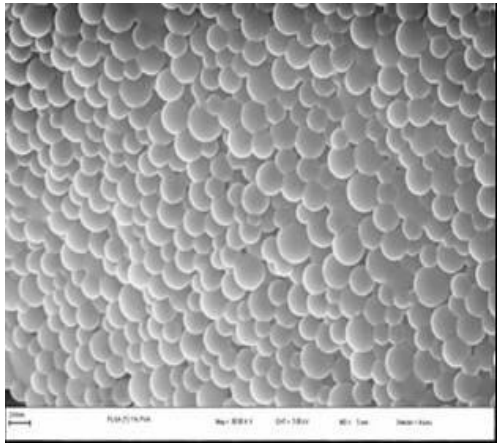


- Improve the PK of anti-TB drugs
  - Sustained release
  - Improve solubility and half-life
- Reduce dose frequency
  - Polymer degradation: Sustained release over days
- Reduce dose
  - Deliver drug at site of action
- Reduce treatment time and cost
  - 6-9 months: potentially 2 months
  - Current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

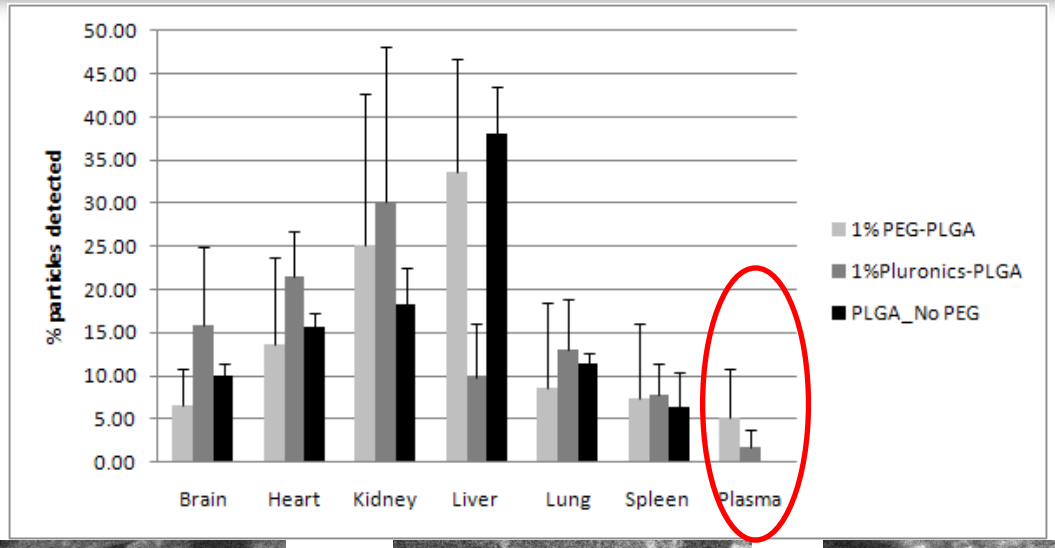
Nanoparticles encapsulating anti-TB drugs (Nanodrug)

- 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

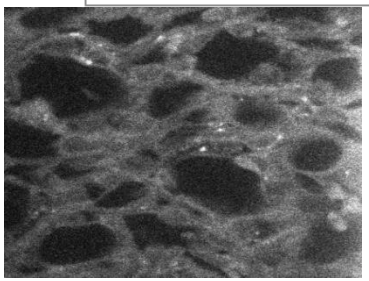
- Properties:
  - 250 nm average size
  - Highly reproducible production
  - Scalable (known pharmaceutical process equipment)
  - Narrow size distribution (polydispersity < 0.1-0.3)
  - Controllable surface charge
  - Modified surface
    - Increase circulation time: PEG
    - Enhance particle uptake: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



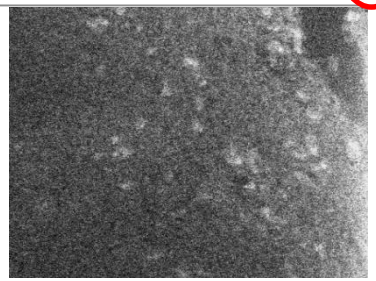
Plasma circulation and biodistribution



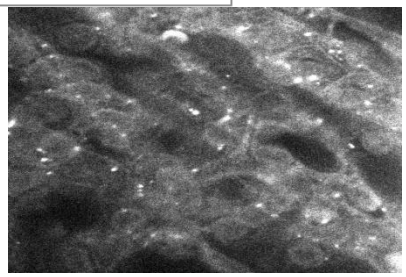
Biodistribution of Rhodamine labelled PLGA nanoparticles coated with 1% PEG or Pluronics F127. 7 days after oral administration.



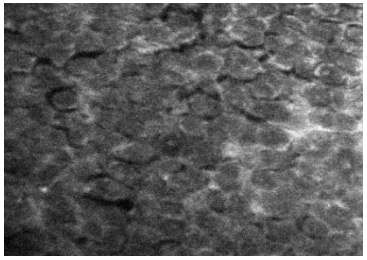
LUNGS



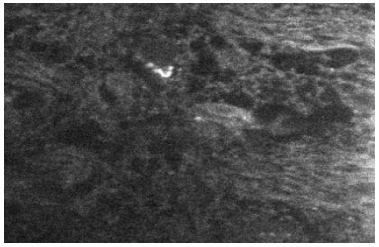
LIVER



KIDNEY

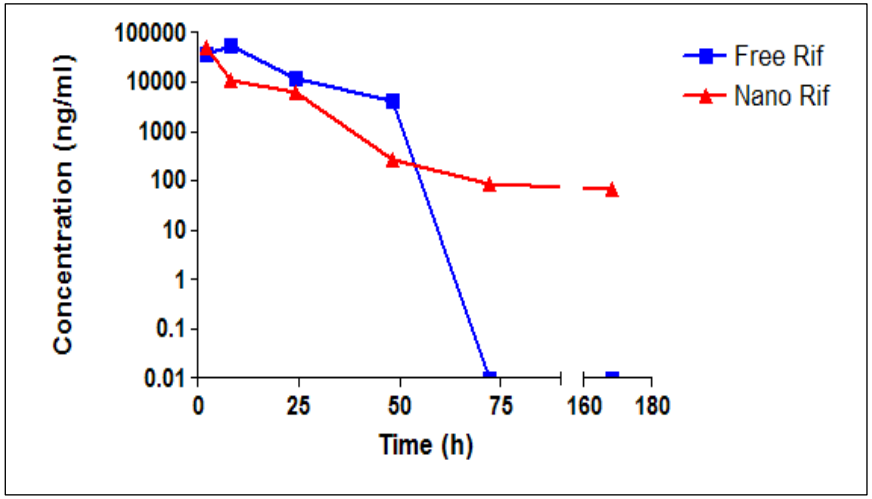


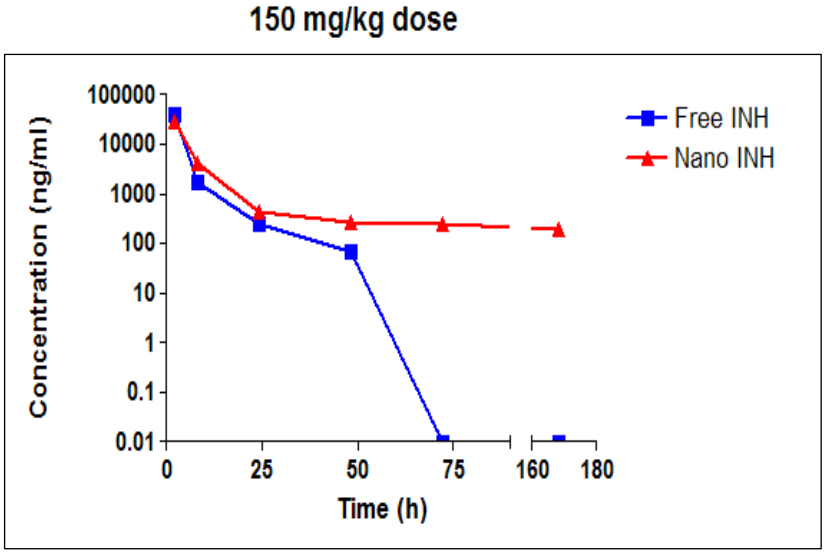
SPLEEN



BRAIN

Pharmacokinetics in unchallenged mice

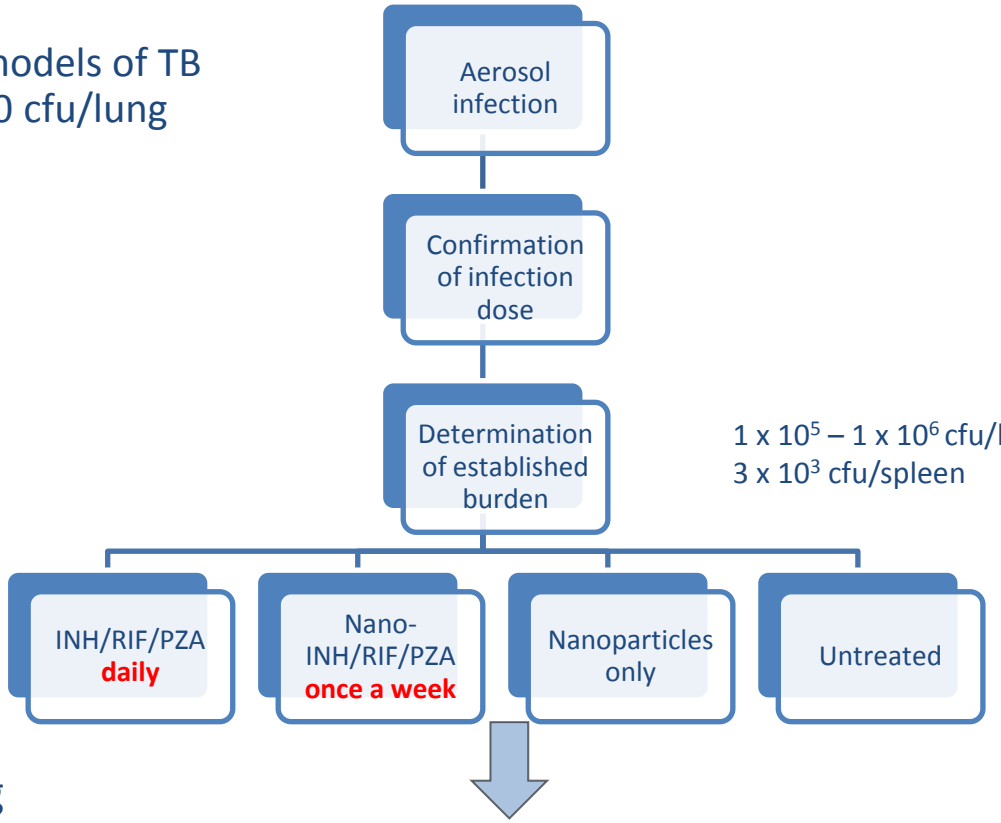




- Sustained release of RIF and INH from PLGA nanoparticles
- Increase in drug half-life
- Potential for dose frequency reduction

How does altered PK affect efficacy?

Female C57BI/6 mice models of TB
H37Rv at 50-100 cfu/lung



Day 0

Day 1

W3

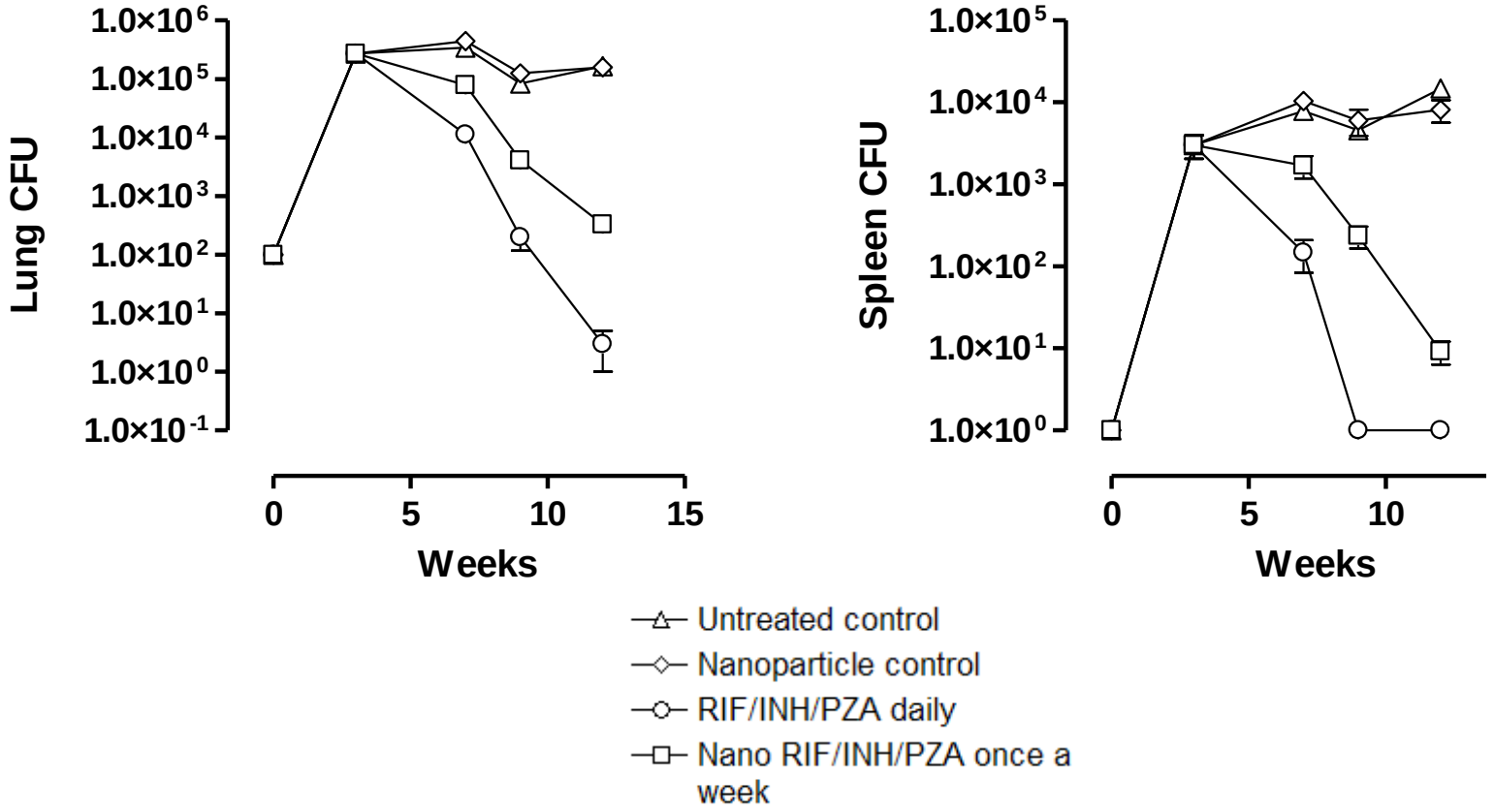
$1 \times 10^5 - 1 \times 10^6$ cfu/lung
3×10^3 cfu/spleen

W7, W9, W12

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

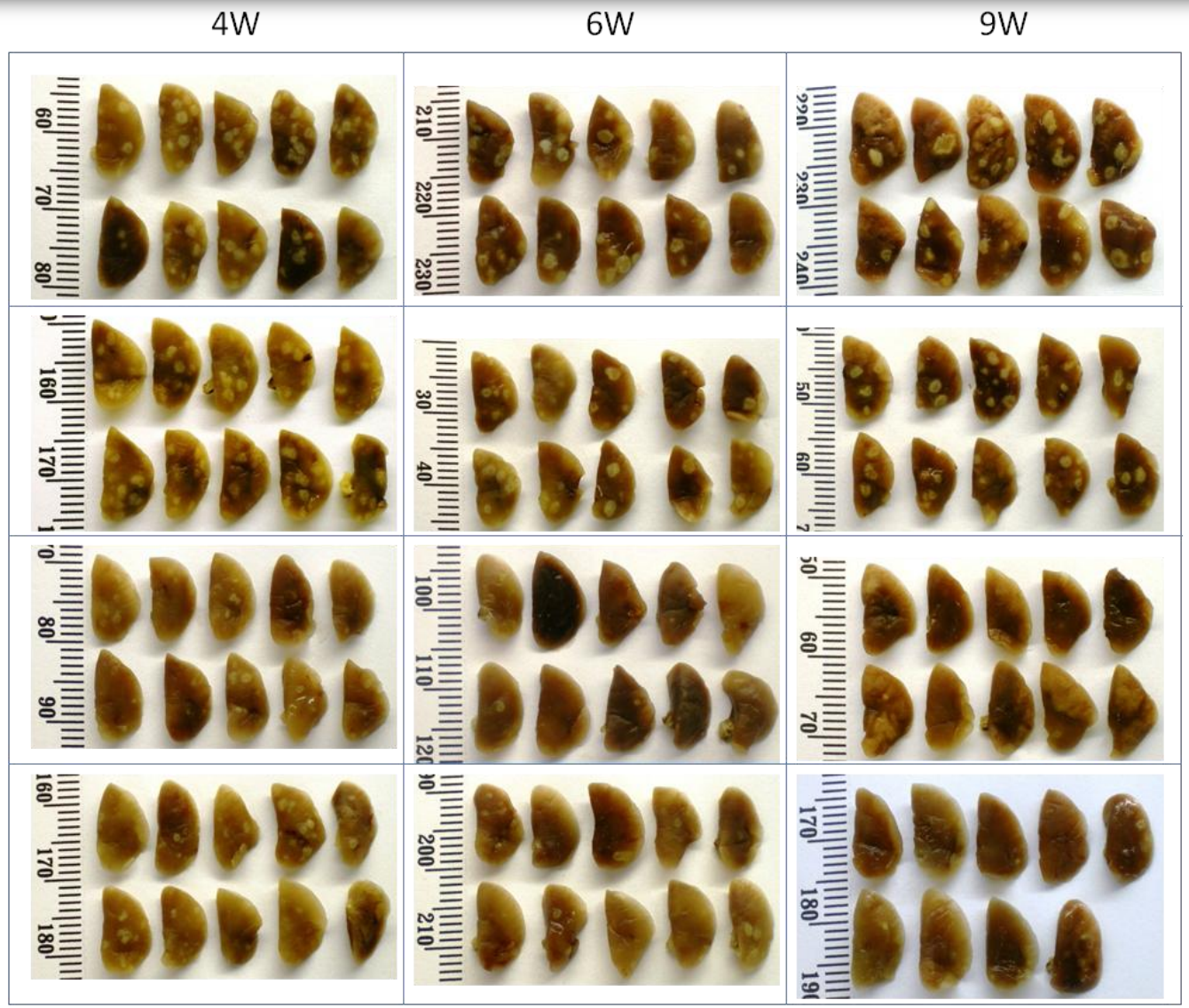
- Data analysis
- Bodyweight (weekly)
- Lung weight
- Pulmonary bacilli burden
- Splenic bacilli burden
- Pulmonary pathology

Effects of the Nanodrug on Mycobacterium tuberculosis replication

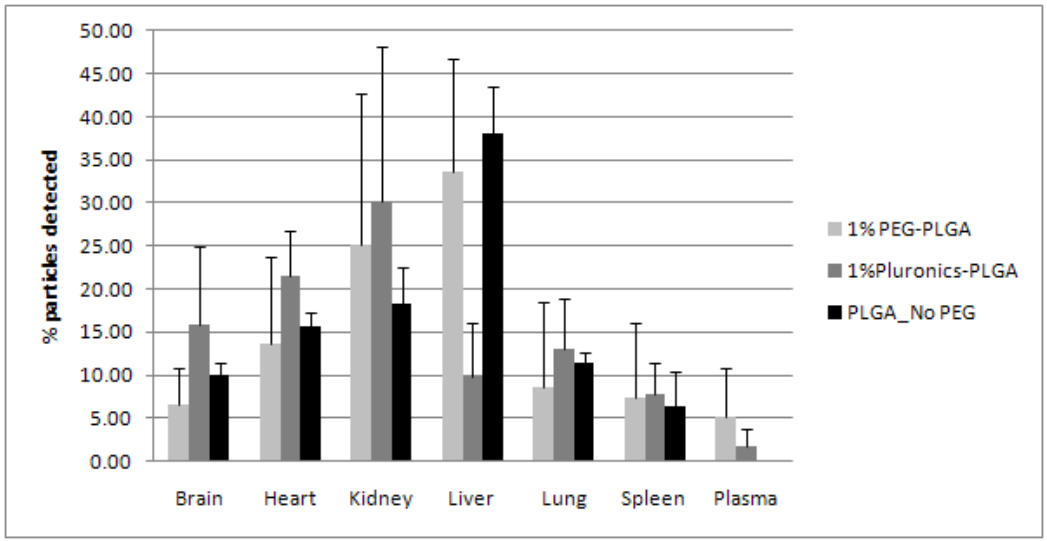


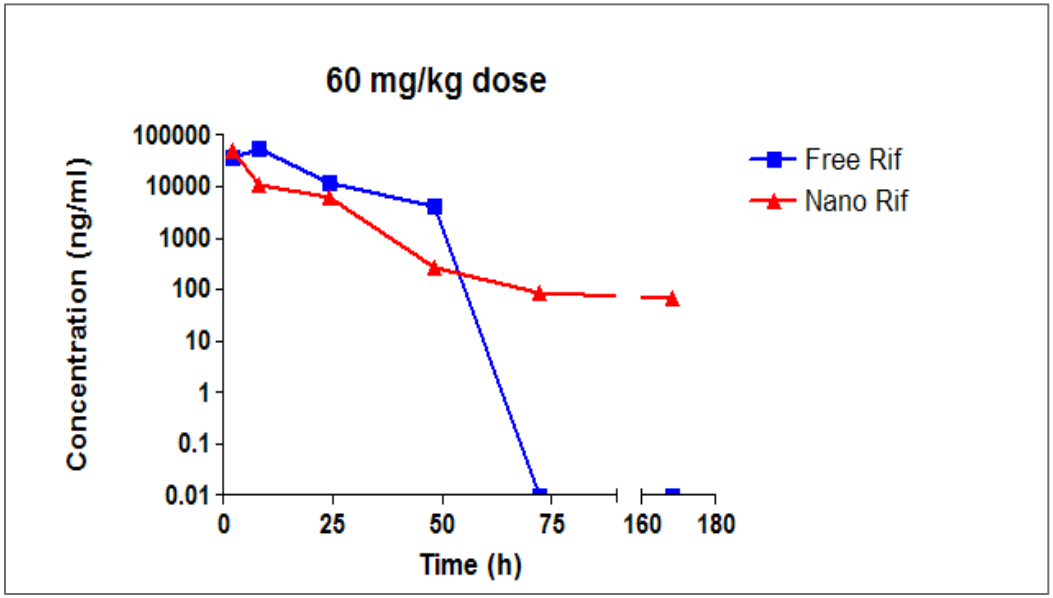
- Nanodrug once a week vs conventional drug daily
- Treatment with nanoencapsulated TB drugs once a week, comparable to daily treatment with conventional drugs

Pulmonary pathology



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

Acknowledgements

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Thank you

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