NANOMEDICINE: RECENT DEVELOPMENTS AND OPPORTUNITIES IN AFRICA

4th Biennial Conference

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Date: 9th October 2012

our future through science

Outline

- 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

Nanomedicine

Nanotechnology:

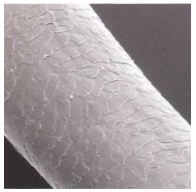
Manipulation of matter at atomic/molecular level

Nanomedicine:

Applications of nanotechnology in health: Mainly for treatment, diagnosis and monitoring of diseases

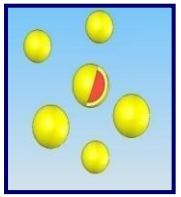
How small

Ant head - 1mm



Human hair - 100um , 100 000 nm

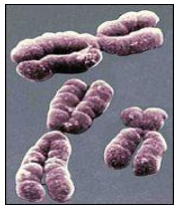
Red blood cell - 10um, 10 000 nm



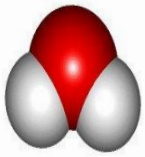
NANOMEDICINE - 100 nm to 500 nm

0.1% of human hair width or

1% of smallest human cell



DNA - 4nm wide



Water molecule - 0.2 nm

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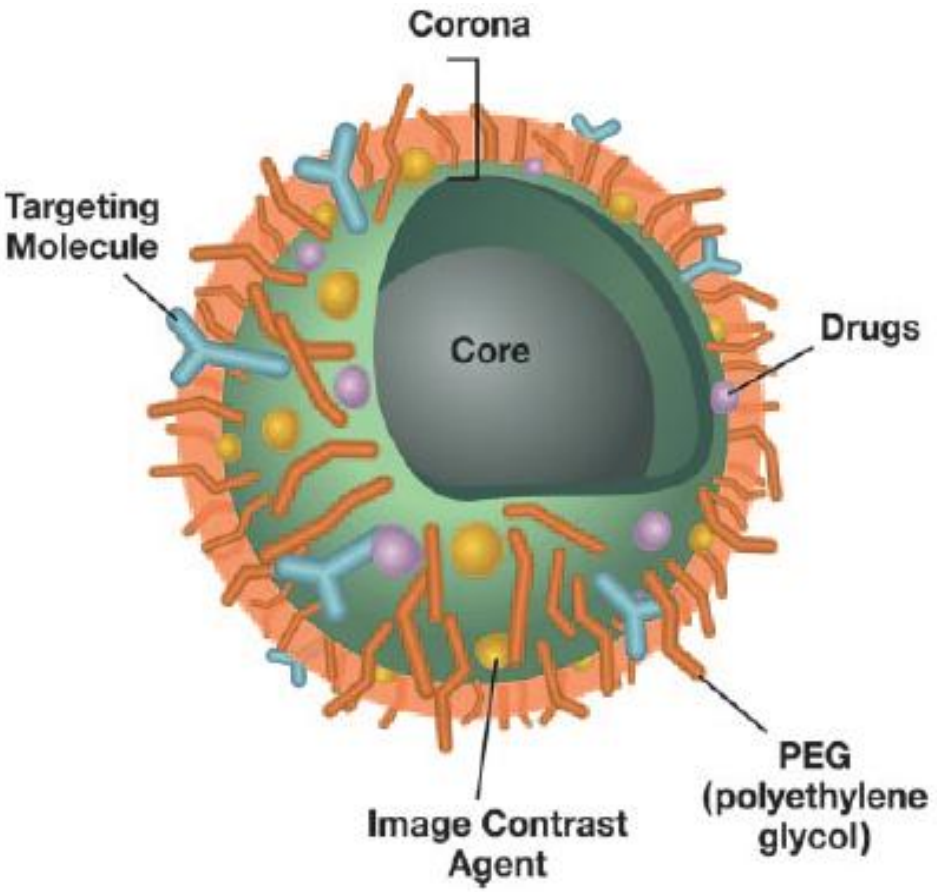
Nanocarriers are multifunctional, targeted devices, capable of crossing all biological barriers to deliver multiple therapeutic agents directly to diseased cells and disease-associated tissues

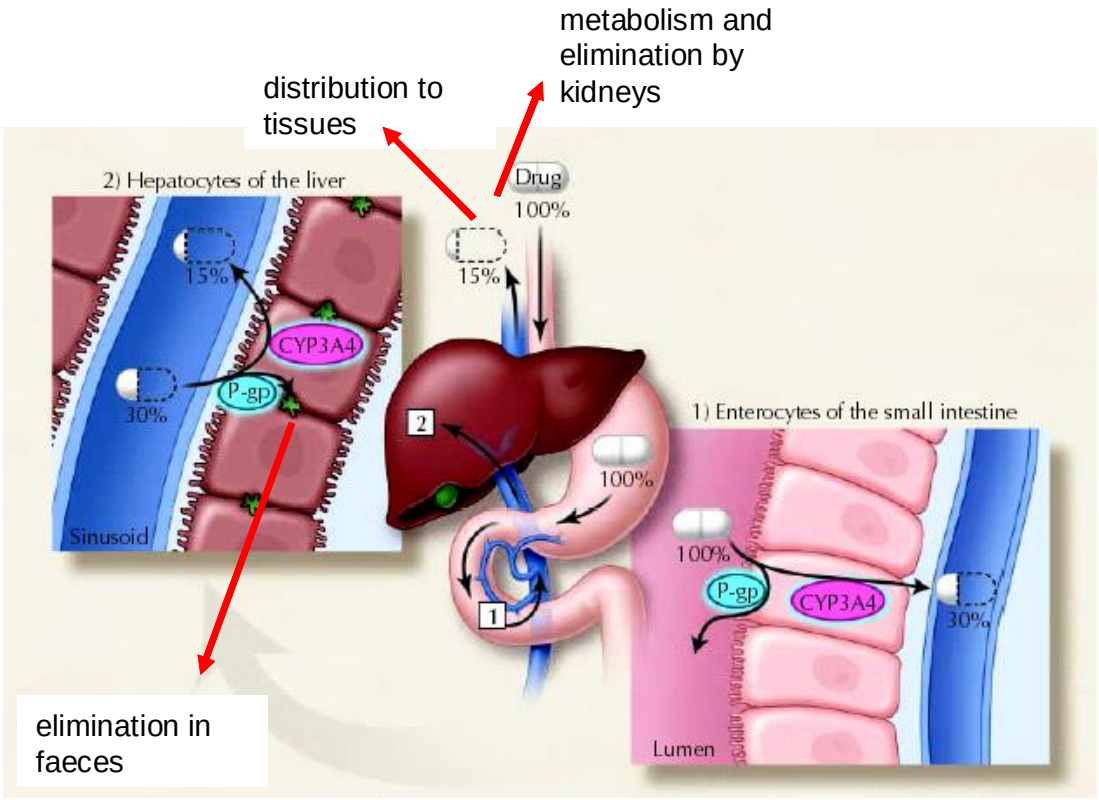
- Size
  - Biological barriers
  - Increased cellular uptake
  - Versatile routes of admin
  - Solubility
  - Large surface area to volume ratio
- Surface
  - Large and active
  - Tailor ability
  - Targeted
    - Early detection
    - Imaging
    - Diagnosis
    - Treatment
    - Disease monitoring
  - Surface charge



McNeil, J Leukocyte Biol. 78:585-594, 2005

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



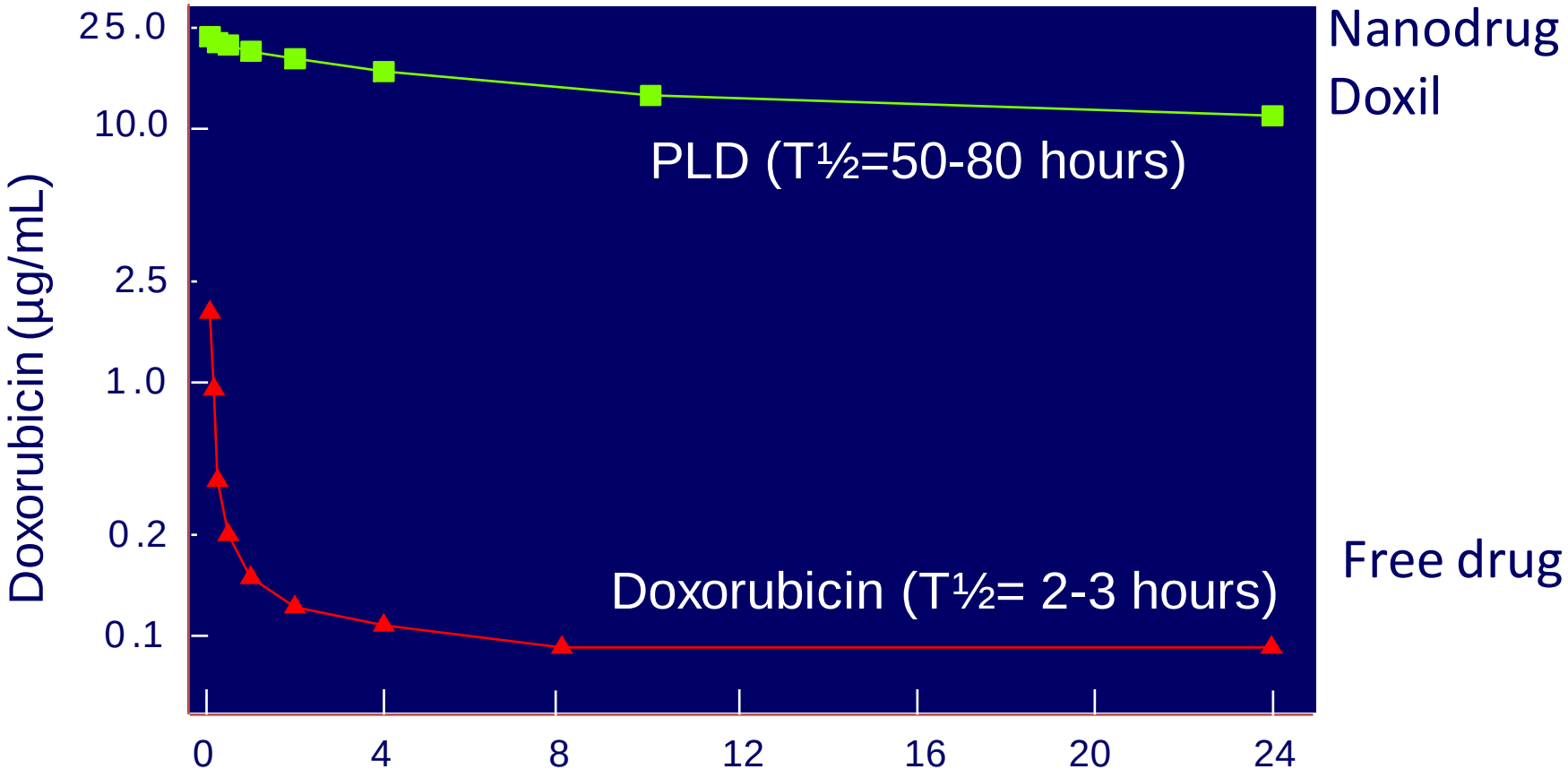
Bailey D.G., and Dresser G.K.; Natural products and adverse drug interactions; *Canadian Medical Association Journal*; 2004: 170(10): 1531-1532.

RECENT DEVELOPMENTS

Pharmacokinetics of Doxil vs Free

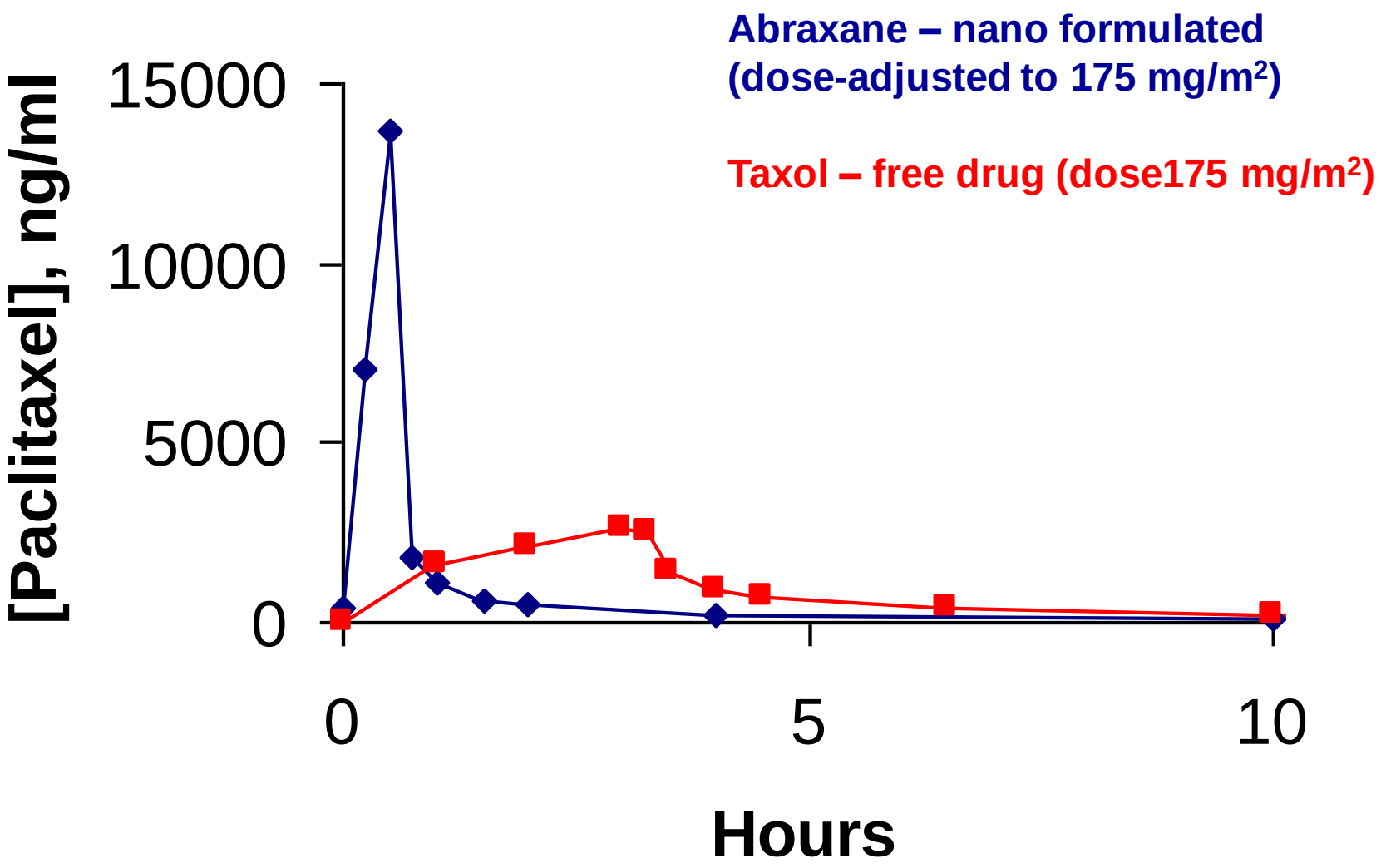
Plasma Levels: tremendous prolonged half-life

(Single Dose, 50 mg/m²)



Gabizon et al., Cancer Res. 1994

Clinical PK Comparison of Total Paclitaxel Study C008-0

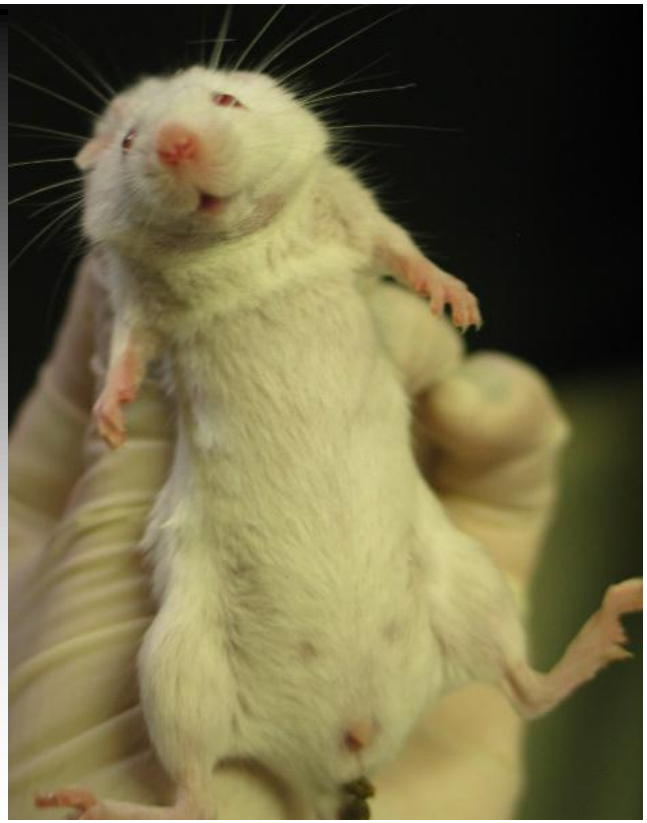


Nanoencapsulated Itraconazole for the treatment of lung fungus

(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

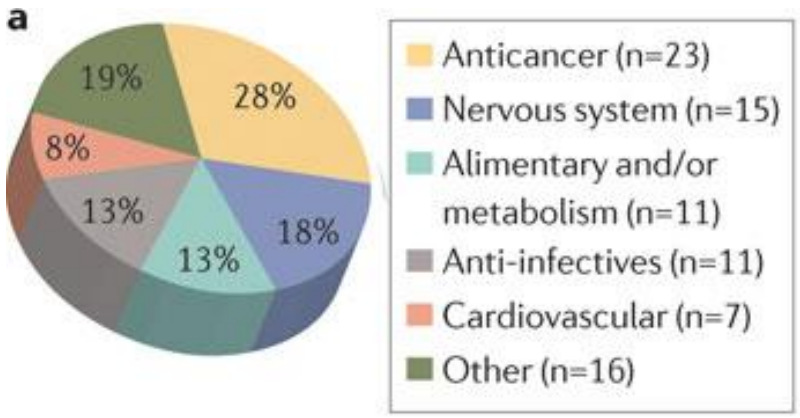
Examples of Nanomedicines already on

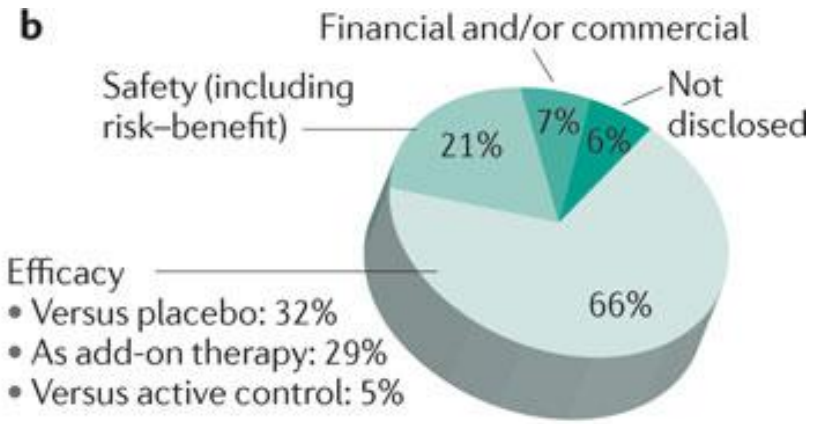
Product	Company	Drug	Formulation	Route of administration	Application
Doxil	Sequus Pharmaceutical	Doxorubicin	Liposome	Intravenous injection	Kaposi sarcoma in AIDS
Amphocil	Sequus Pharmaceutical	Amphotericin B	Lipocomplex	IV infusion	Serious fungal infections
Ambisome	NeXstar Pharmaceutical	Amphotericin B	Liposome	IV infusion	Serious fungal infections
DaunoXome	NeXstar Pharmaceutical (Boulder, Colorado)	Daunorubicin citrate	Liposome	IV	Kaposi sarcoma in AIDS
Abelcet	The Liposome Company (Princeton, New Jersey)	Amphotericin B	Lipid complex	IV infusion	Serious fungal infections
Rapamune	Wyeth/Elan (Madison, New Jersey)	Sirolimus	Nanocrystal particles	Oral	Immunosuppressant in kidney transplant patients
Emend	Merck/Elan (Whitehouse Station, New Jersey)	Aprepitant, MK869	Nanocrystal particles	Oral	For chemotherapy patient to delayed nausea and vomiting
TriCor	Abbott (Abbott Park, Illinois)	Fenofibrate	Nanocrystal particles	oOral	Primary hypercholesterolemiamixed lipidemia, hypertriglyceridemia
Megace ES	PAR Pharmaceutical (WoodCliff Lake, New Jersey)	Megaestrol acetate	Nanocrystal particles	Oral	Treatment of anorexia, cachexia, or an unexplained significant weight loss in patients with a diagnosis of AIDS
Abraxane	American Biosciences (Blauvelt, New York)	Paclitaxel	Albumin-bound nanoparticles	IV injection	Metastatic breast cancer
Elestrin	BioSante (Lincolnshire, Illinois)	Estradiol	Calcium phosphate–based nanoparticles	Transdermal	Treatment of moderate-to-severe vasomotor symptoms (hot flashes) in menopausal women

Bawarski et al., Nanomedicine: Nanotechnology, Biology, and Medicine 4:273–282, 2008

POTENTIAL OF NANOMEDICINE IN DRUG DEVELOPMENT

Potential of Nanomedicine in drug development programs





FDA Phase III and submission failures, 2007-2010

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

Example of PRD Drug Development: TB Drug

TB drug pipeline (TB global alliance)

	Phase 1	Phase 2	Phase 3
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**

it's been 40 years since the last new drug, yet only 2 drugs going through phase III clinical trials!

Novartis cancer drug pipeline

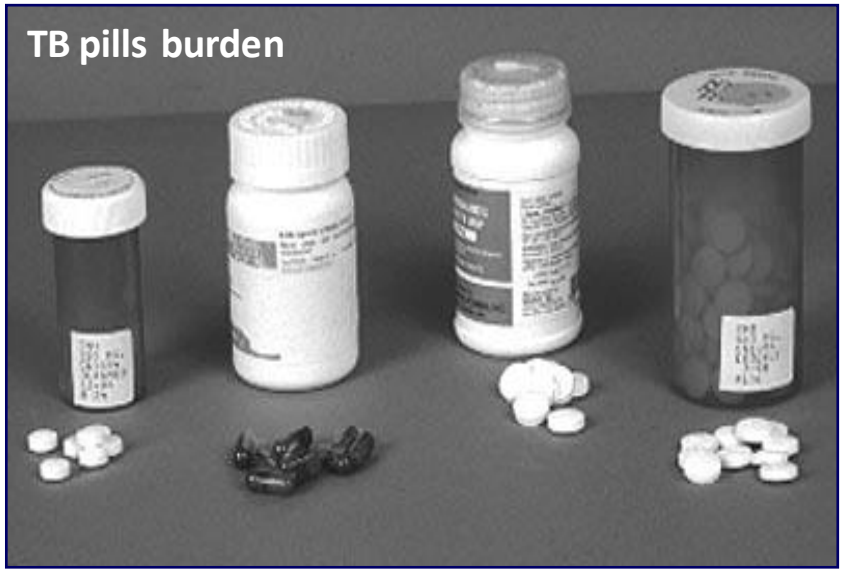
PHASE I/II	PHASE III
Midostaurin ASM[1]	**INC424**[f] Myelofibrosis
Dovitinib[d] Solid & Hemat. tumors	**Panobinostat** Hodgkin's lymphoma
RAF265 Solid tumors	**Midostaurin** AML[3]
Lucatumumab[e] Hemat. tumors	**Everolimus** HCC[7]
BEZ235 Solid tumors	**Everolimus** TSC AML[5]
BKM120 Solid tumors	**Everolimus** ER+ & HER2+ Breast Cancer
LDE225 Solid tumors	**Everolimus** Gastric cancer, Lymphoma
Deferasirox NTDT[2]	**Pasireotide**[g] Acromegaly and Carcinoid
Deferasirox Hered. Hematochrom.	**Nilotinib** GIST[6] & cKIT Melanoma
Panobinostat[c] Hemat. tumors	**Panobinostat**[c] Multiple Myeloma
Everolimus Solid tumors	**INC424**[f] Polycythemia Vera**

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

TB AND MALARIA AS A CASE STUDY

South Africa TB Statistics

- 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)



Daily intake of antibiotics

WHO report: 2005

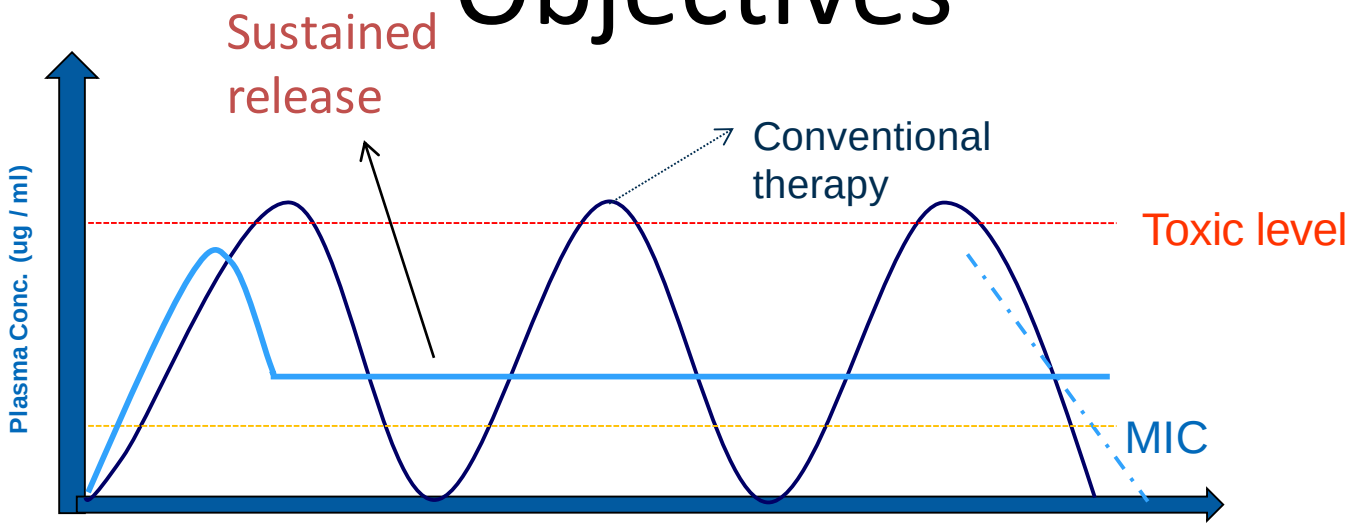
TB treatment: Main challenges in

14 Tablets for 2 years

1 injection daily for 6 months

- **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

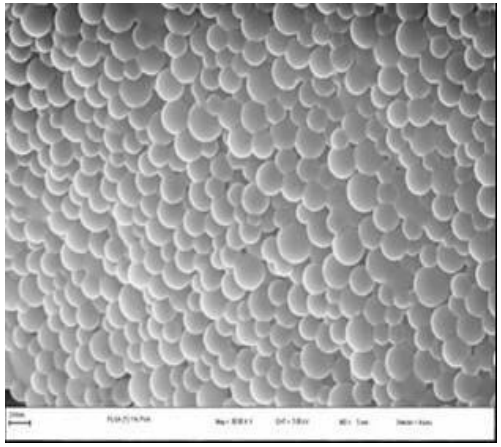


- Improve the bioavailability of anti-TB drugs
  - Nanocapsule: slow release
  - Minimise drug-drug interactions
  - Improve solubility and half-life
- Reduce dose
  - Size: improve biodistribution
- Reduce dose frequency
  - Polymer degradation: Sustained release over days
- Reduce treatment time and cost
  - 6-9 months: potentially 2 months
  - Current drugs cost: 1% of the total treatment management

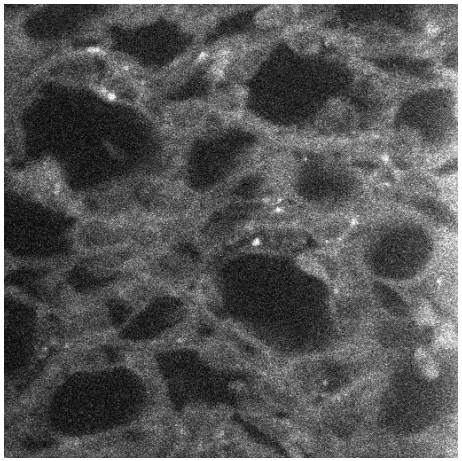
OUR PROGRESS

Project technical status

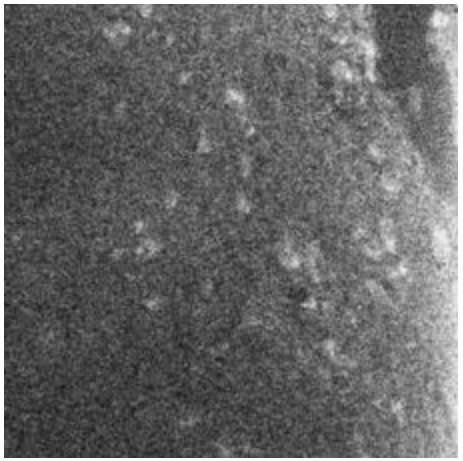
- Successfully nano encapsulated 4 of first line anti-TB drugs
  - Using double emulsion solvent evaporation - spray drying technique
  - PCT patent application filed
- Properties:
  - 200 nm average size
  - Highly reproducible production
  - Scalable (known pharmaceutical process equipment)
  - Narrow 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 and other PRDs
    - Other products like cosmetics, fertilizer and veterinary medicine



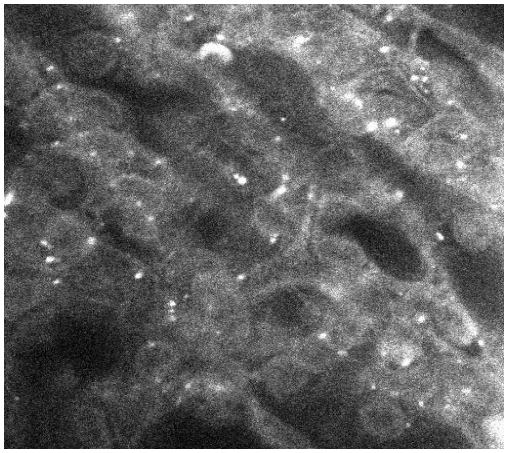
Where the TB nanomedicines go in



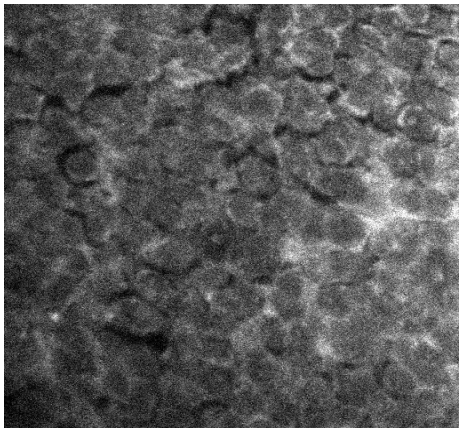
LUNGS



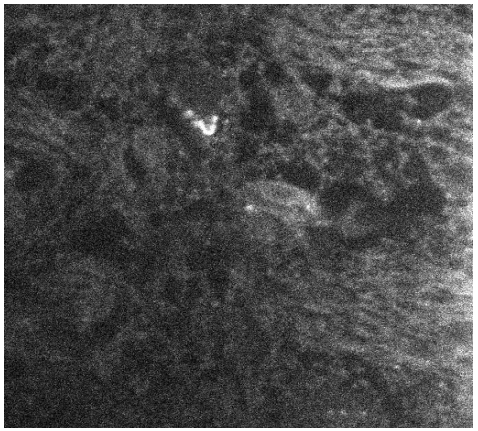
LIVER



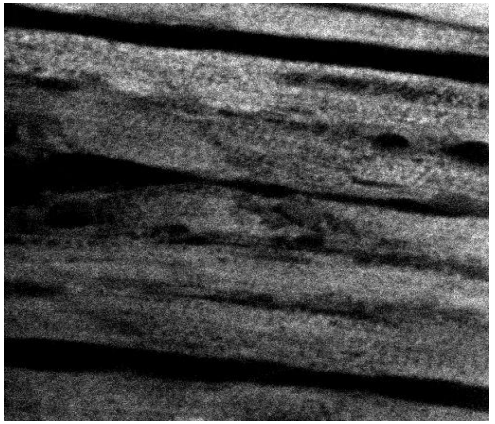
KIDNEY



SPLEEN

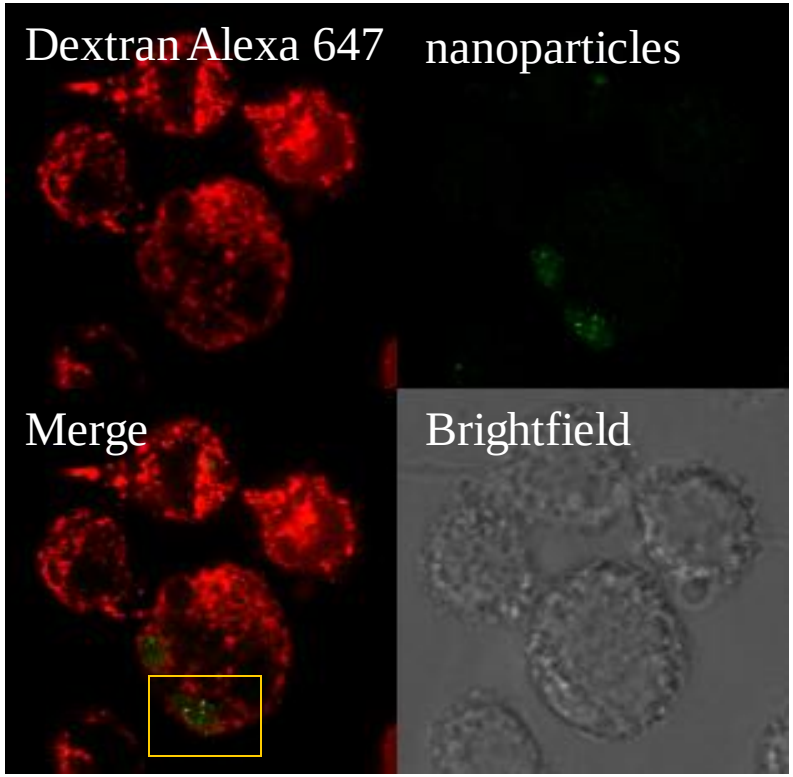


BRAIN

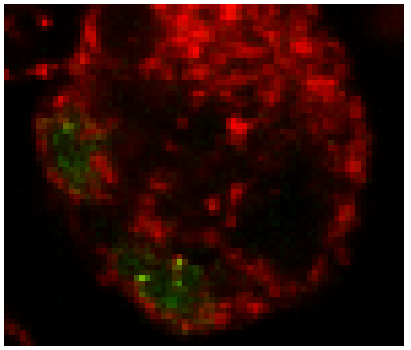


HEART MUSCLES

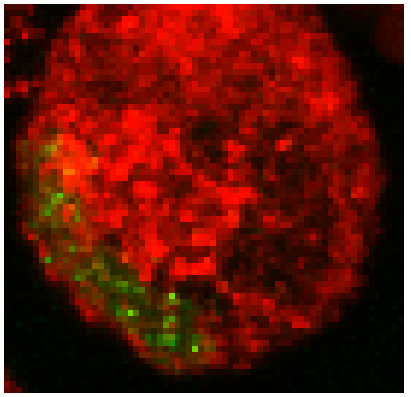
Particles are mobile within the cell



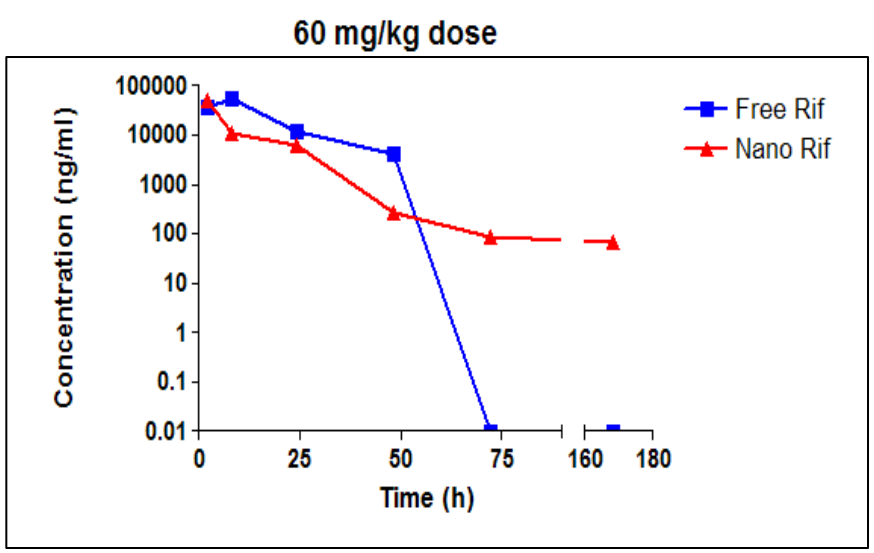
single section

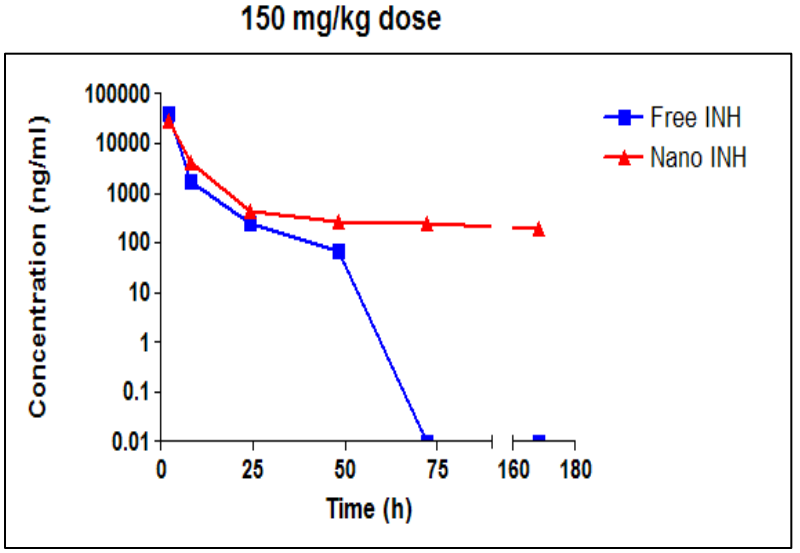


maximum projection



In vivo release, Swai *et al* unpublished data

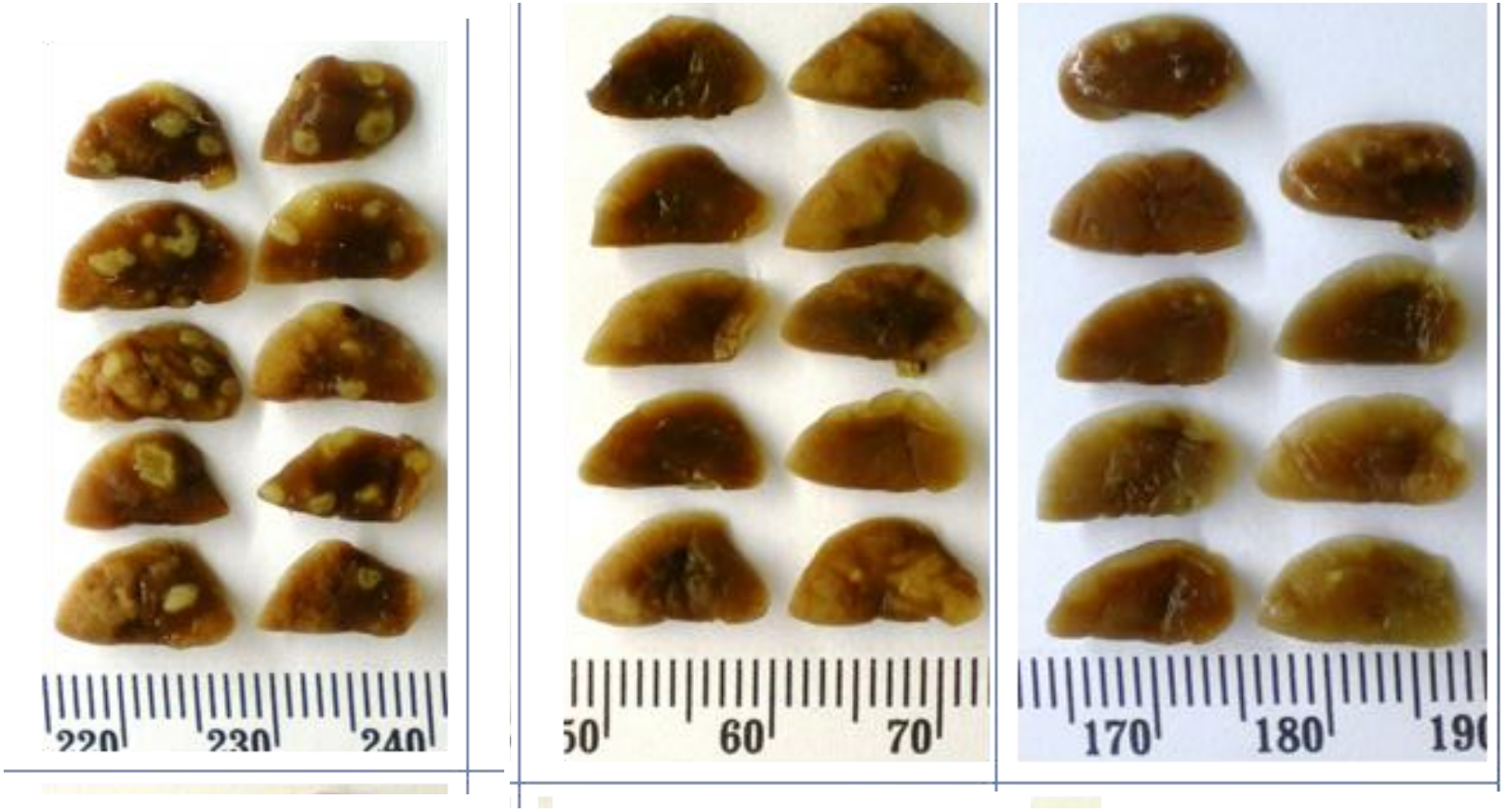




- Increase in drug half-life
- PK of RIF and INH show slow release

Lung pathology- TB nanomedicine vs normalTB

- Encapsulated INH/RIF administered once a week vs free RIF/INH administered daily
- comparable reduction in lung lesions with reduced dose frequency



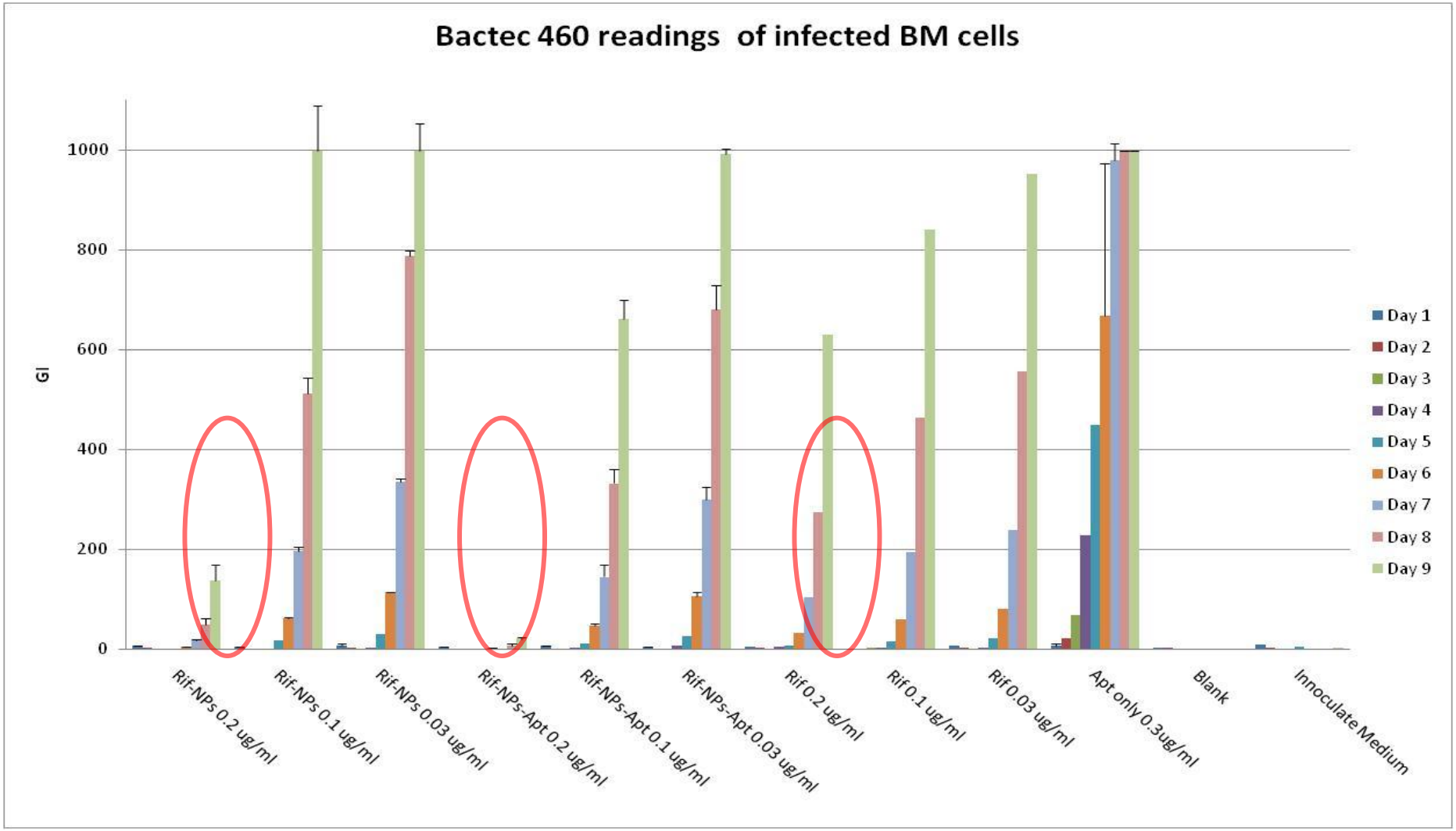
Untreated mice

normal TB medicine DAILY

TB nanomedicine ONCE A WEEK

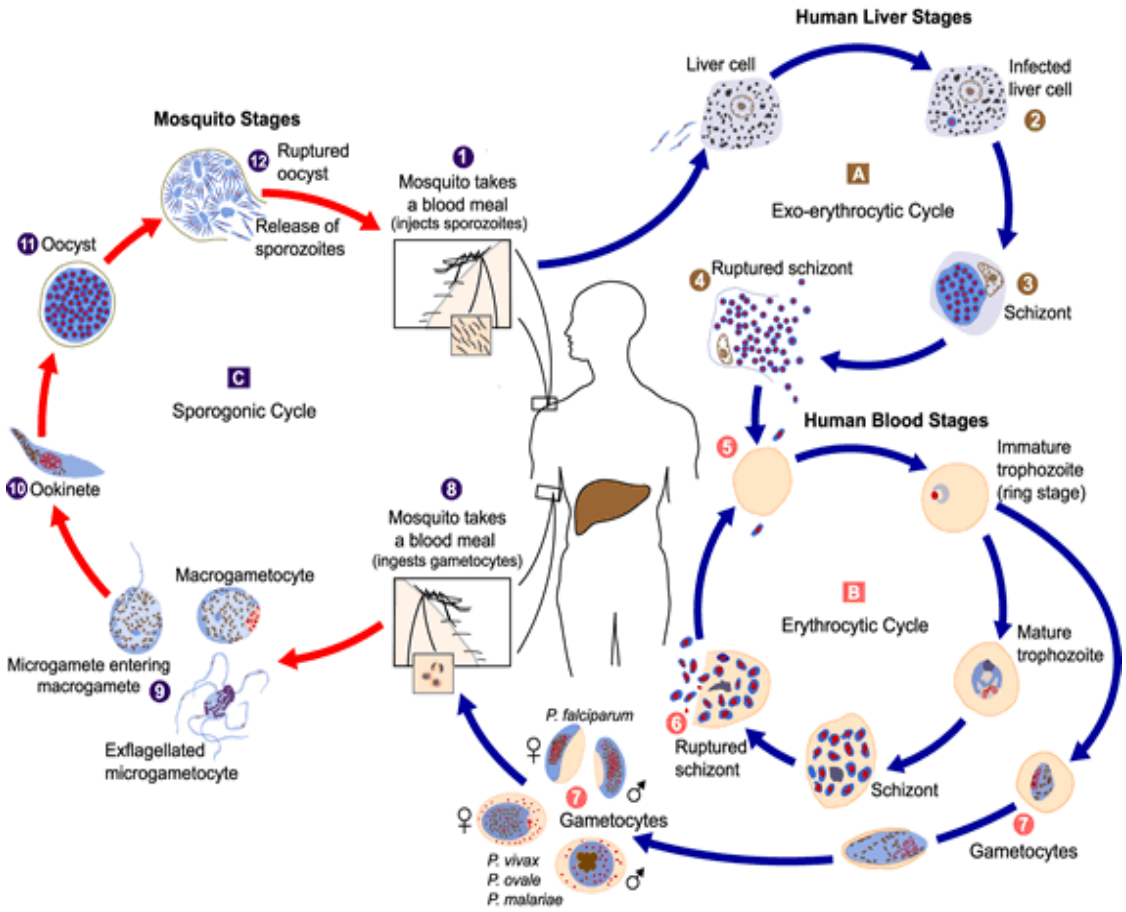
Efficacy of aptamer conjugated nanoparticles of Rifampicin

- *in vitro* superiority of targeted nanoparticles



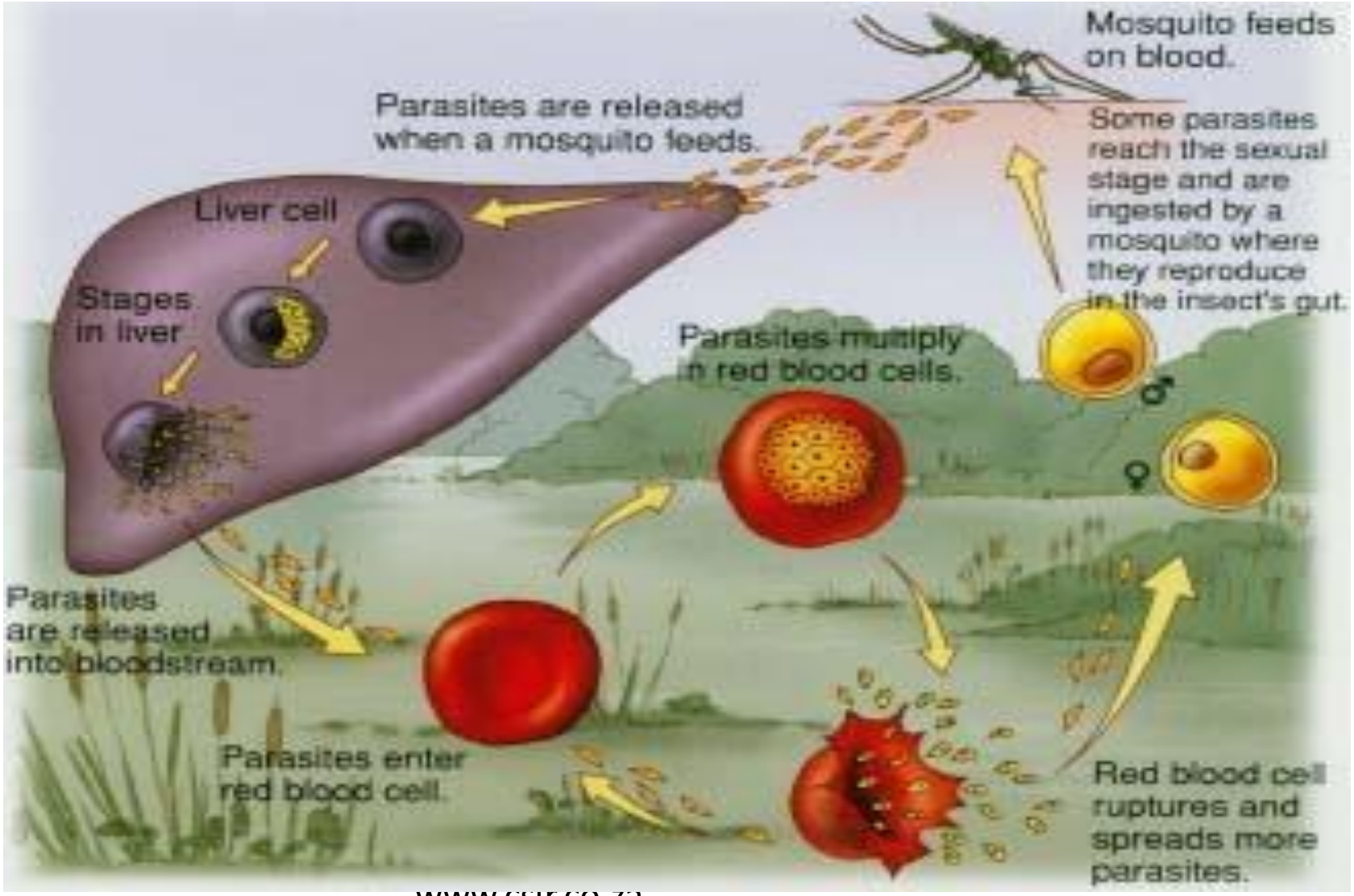
Nanomedicine for Malaria- Prevention

- 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

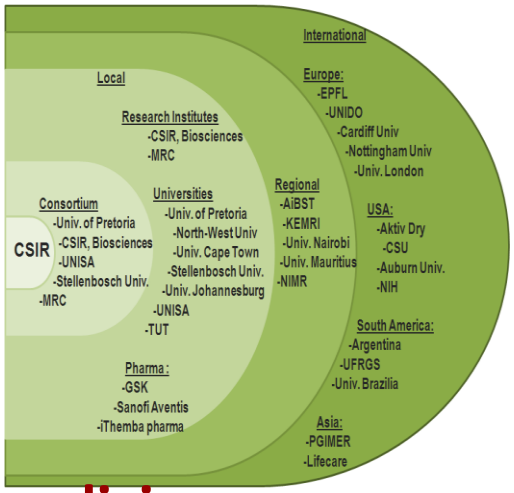
State of the art laboratories

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

Public engagement

Nanomedicine for TB project

International collaboration



- **Pan-African Centre of Excellence in Nanomedicine**

science & technology
Department:
Science and Technology
REPUBLIC OF SOUTH AFRICA

CSIR
our future through science

ANDi
Health Innovation for Development

Nanomedicine Workshop for Poverty Related Diseases:

- 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

Nanomedicine CoE Research Team at CSIR

Thank you

our future through science

Targeting nanoencapsulated anti-TB drugs to sites of infection:

Mycolic acid and aptamer ligands for drug targeting

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