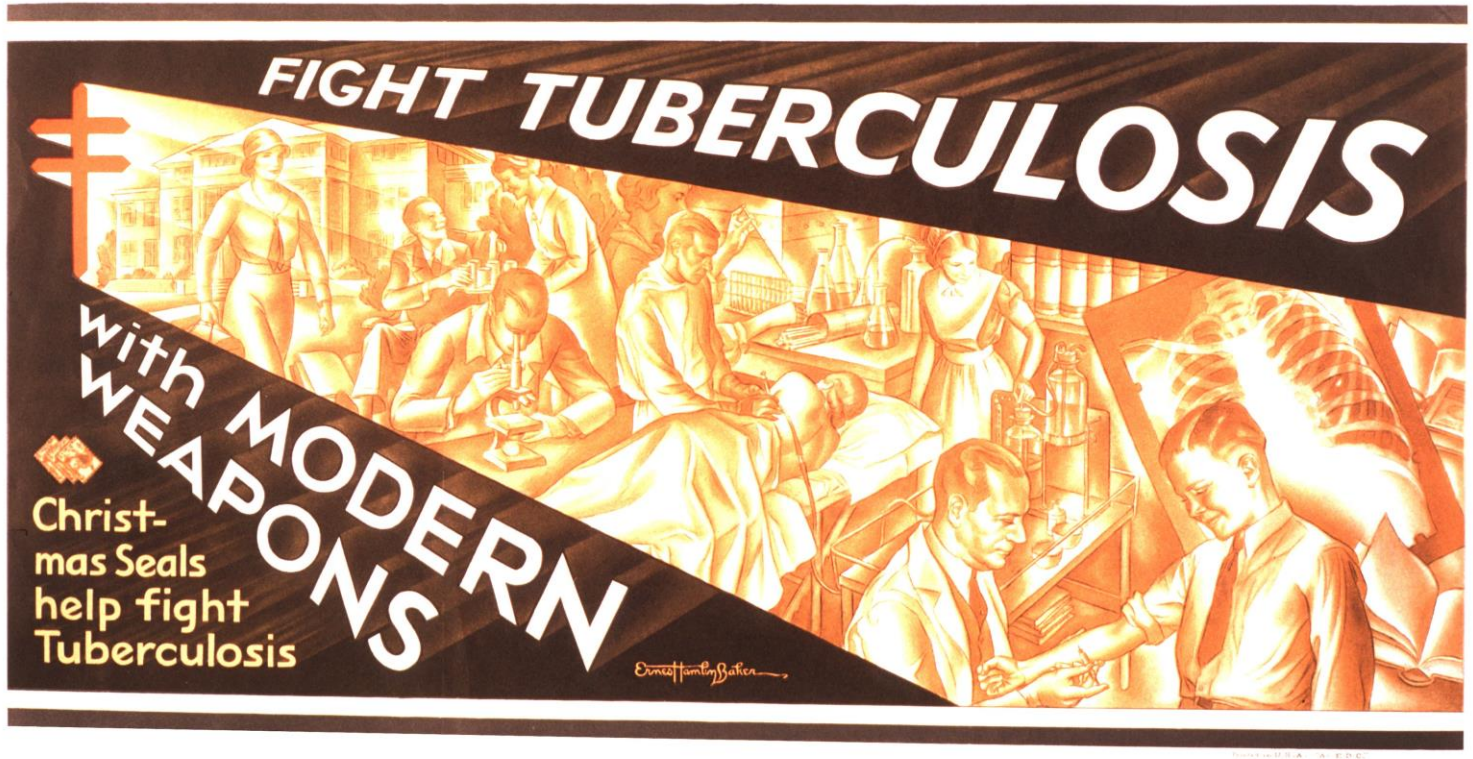
Long acting agents for tuberculosis



Marco Siccardi, Ph.D

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UNIVERSITY OF LIVERPOOL

Overview

- Pharmacokinetic and pharmacodynamic considerations of long acting therapy
- Identification of relevant drug characteristics
- Modelling and simulation for the selection of lead candidates
- Preliminary results in pre-clinical models
- Future development and perspectives

Potential advantages for LA TB

- Less frequent dosing
- Oral dosing bypassed; bioavailability ~100%
- Less adverse events
- Drug-drug interactions
- Improved adherence
- Easier DOT
- May improve tissue penetration, eg lung, lymphatics

Screening of potential LA candidates

PHARMACOKINETICS

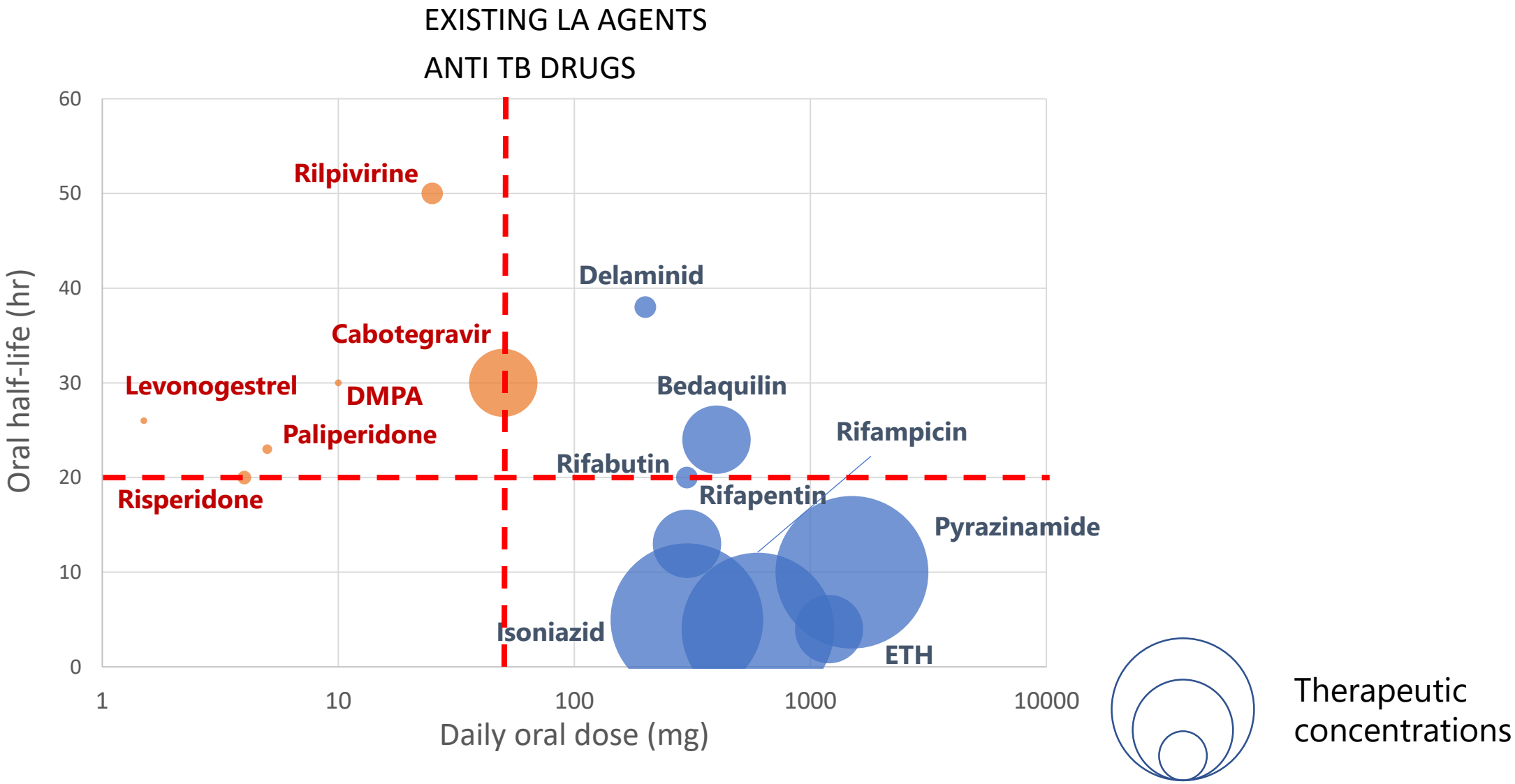
- Long half life
- Good penetration in tissues and organs
- Suitable volume of distribution
- Low induction or inhibition potential

PHARMACODYNAMICS

- Therapeutic protocol based on monotherapy or simple combination
- Favourable PK/PD relationship and high potency

Sustained therapeutic concentrations of APIs through controlled release from formulations (i.e injectables, implants, etc).

Posology, pharmacokinetic and pharmacodynamic characteristics of LAIs – choice of agent



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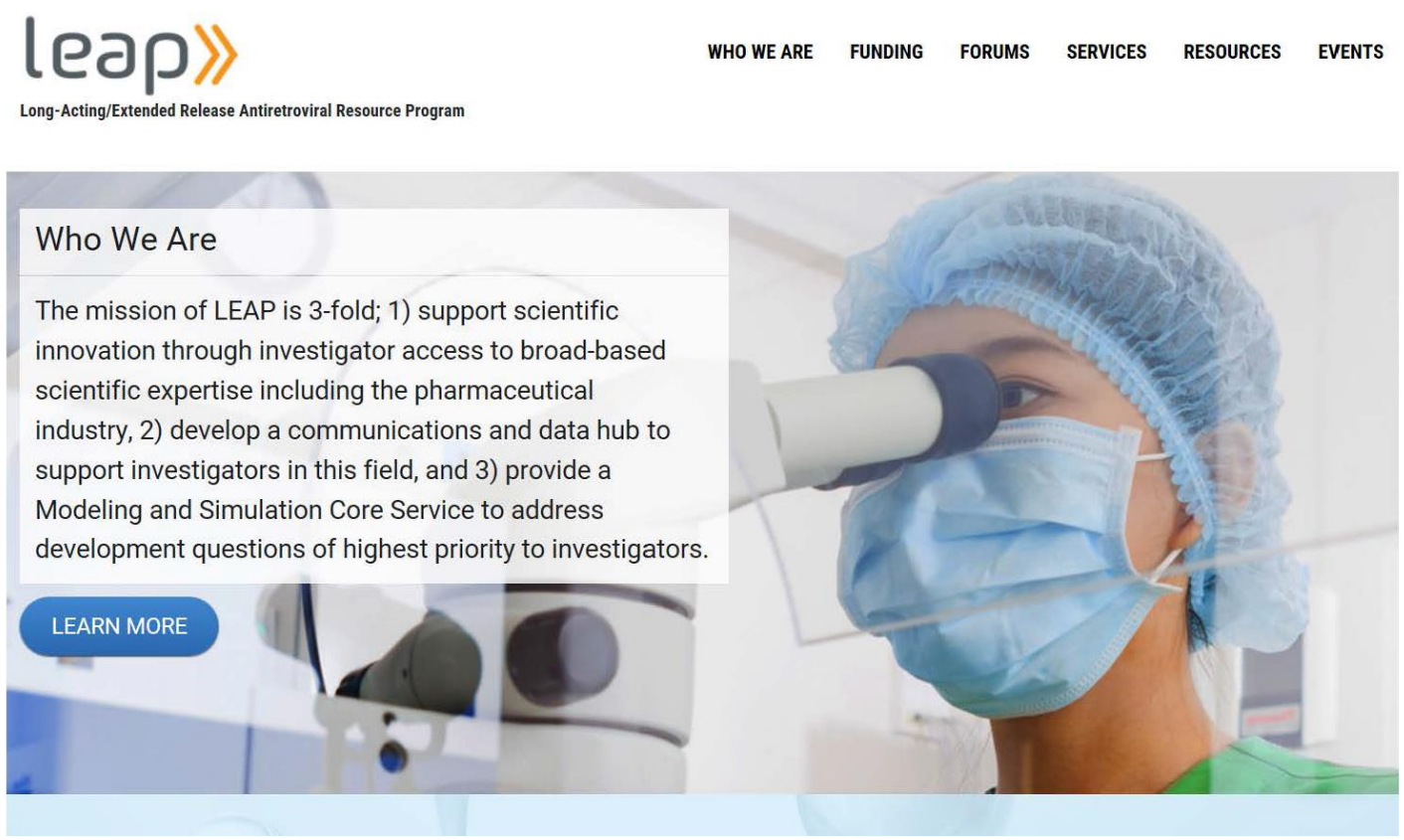

TB LEAP Membership

Susan Swindells (chair)	U of Nebraska
Charles Flexner (grant PI)	Johns Hopkins
Stephanie Barrett	Merck
Tine De Marez*	J&J
Kelly Dooley	Johns Hopkins
Jay Grobler	Merck
Daria Hazuda	Merck
Richard Hoetelmans*	J&J
Daniella Livnat	DAIDS, NIH
Gary Maartens	U of Cape Town
Eric Nuermberger	Johns Hopkins
David Olsen	Merck
Andrew Owen	U of Liverpool
Anthony Podany	U of Nebraska
Kimberly Scarsi*	U of Nebraska
Marco Siccardi	U of Liverpool

Goals:

1) formation of an expert task force to prioritize research areas for HIV/TB coinfection,
2) to develop a Target Product Profile for potential long-acting/extended release drugs that can be used by investigators and regulators working in this area; and
3) support for a Working Group to promote screening and identification of promising agents for such applications, including the re-purposing of agents already screened for other bacterial diseases.

Target Product Profile for a TB LA/ER formulation

	Indication/ Mechanisms	Route of administration	Efficacy	Side effects, and safety	Shelf-life and storage and cost of treatment
Minimal	Treatment of presumed drug susceptible latent TB	IV infusion; IM/SC injection; or implantation	Non-inferior to SOC (e.g. RPT/INH - 3mo)	DDIs no worse than current therapy; mild injection site reaction	2 yr at 4°C; Total health system cost no greater than current
Ideal	Treatment of latent TB infection, including for contacts of MDRTB	IM/SC; or implantation	Superior to SOC (less incident TB, shorter duration of treatment)	No significant side effects; no significant DDIs; safe for use in pregnant and lactating women; no injection site reaction	3 yr at 40°C and 75% humidity; Total health system cost less than current

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Modelling the long-acting administration of anti-tuberculosis agents using PBPK: a proof of concept study

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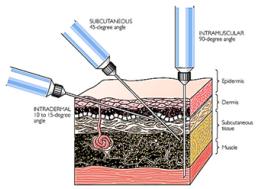
*Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, UK; †College of Pharmacy, University of Nebraska Medical Center, Omaha, Nebraska, USA; ‡School of Pharmacy, Keele University, Newcastle, UK; §College of Medicine, University of Nebraska Medical Center, Omaha, Nebraska, ¶Johns Hopkins University School of Medicine and Bloomberg School of Public Health, Baltimore, Maryland, USA

Intramuscular release rate

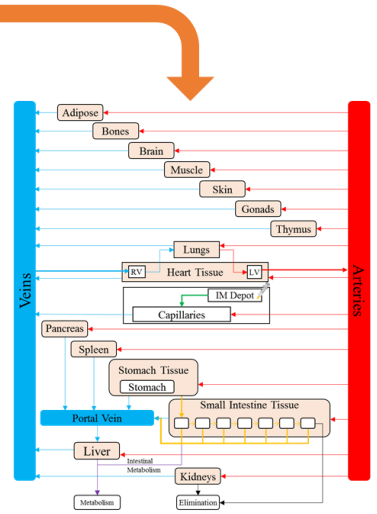


Metabolic clearance

Volume of distribution

$$V_{ss} = (\Sigma V_t^* P_{t:p}) + (V_e^* E{:}P) + V_p$$

$$P_{t:p\,nonadipose} = \frac{[P_{o:w} \times (V_{nlt} + 0.3 \times V_{pht})] + [1 \times (V_{wt} + 0.7 \times V_{pht})]}{[P_{o:w} \times (V_{nlp} + 0.3 \times V_{php})] + [1 \times (V_{wp} + 0.7 \times V_{php})]} \times \frac{fu_p}{fu_t}$$



Pharmacokinetics

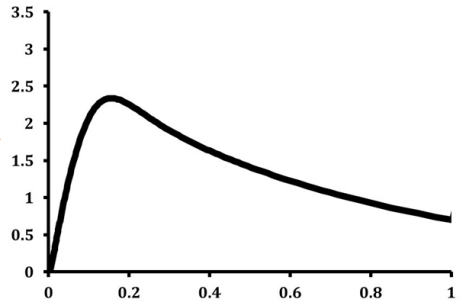
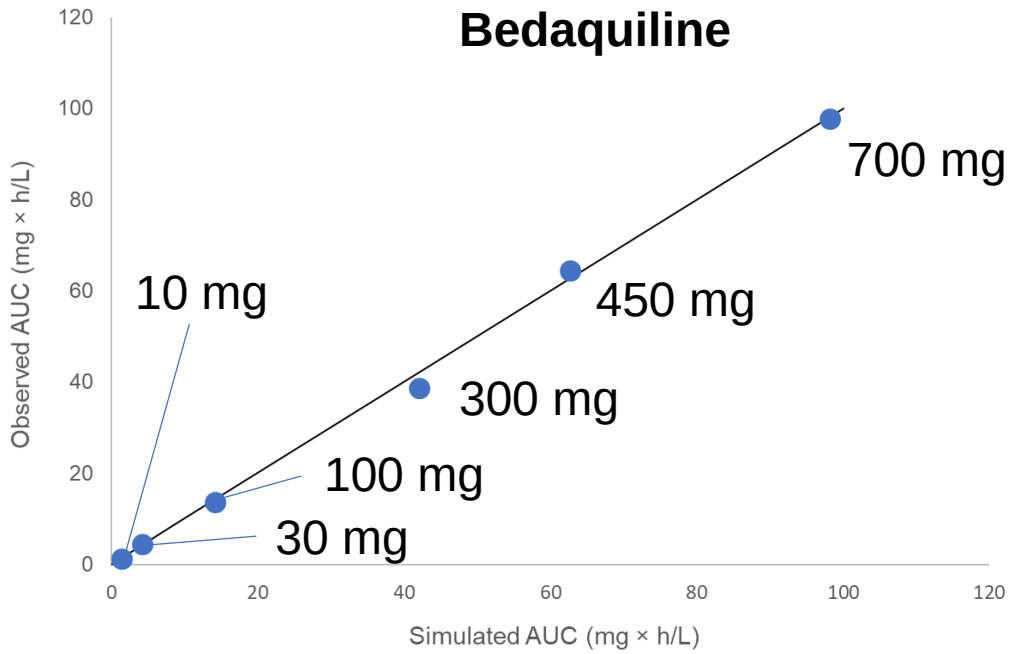


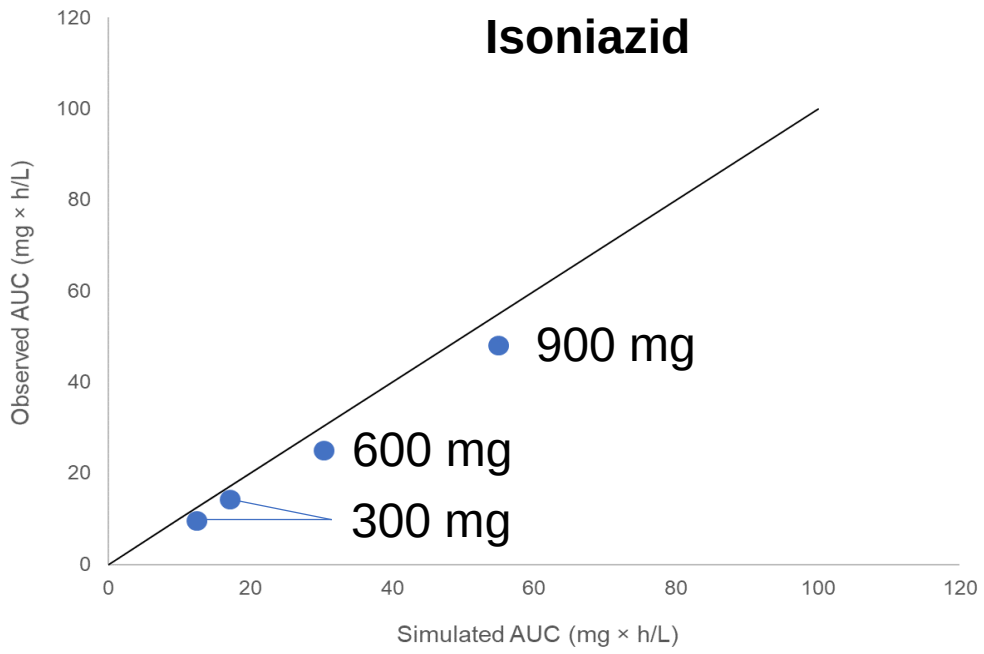
Table 1 Physicochemical properties and in vitro and population pharmacokinetic data of anti-tuberculosis drugs

	Bedaquiline	Delamanid	Isoniazid	Rifapentine
log $P_{o:w}$	6.37[14]	5.53[15]	–0.7[16]	4.0[17]
pKa	13.61, 8.91[14]	3.99[15]	1.82[16]	7.17, 7.01[17]
Blood-to-plasma ratio	4.04*	3.92*	0.80*	0.56[18]
Protein binding, %	99.9[14]	99.55[19]	10[16]	97.7[17]
Plasma clearance, l/h/kg	0.04 ± 0.002[20]	0.729 ± 0.121[21]	0.142 ± 0.042[22†]	0.028 ± 0.009[23]
Absorption rate, h^{-1}	1.03 ± 0.19[24]	0.96[25‡]	2.28[22]	0.42[25§]
V_d, l/kg	2.18[20]	7.32[21]	0.21[26]	0.69[23]
Bioavailability, %	100[20¶]	36 (25–47)[21]	100[22¶]	45 (40–50)[27#]

* Blood-to-plasma ratios were computed using equations from Paixão et al.[28]
† Value provided is apparent clearance of slow acetylators.
‡ Computed from polar surface area and hydrogen bond donor values using the equation from Gertz et al.[29]
§ Computed from Caco-2 permeability using the equation from Gertz et al.[29]
¶ Bioavailability has been fixed to 100 in the population pharmacokinetic studies.
# A bioavailabity of 40–50% was assumed based on the relative bioavaiility of 70% for the oral formulation using the oral formulation as a reference.
log $P_{o:w}$ = partition coefficient between octanol and water; pKa = logarithmic value of the dissociation constant; V_d = volume of distribution

PBPK model qualification against available oral PK data

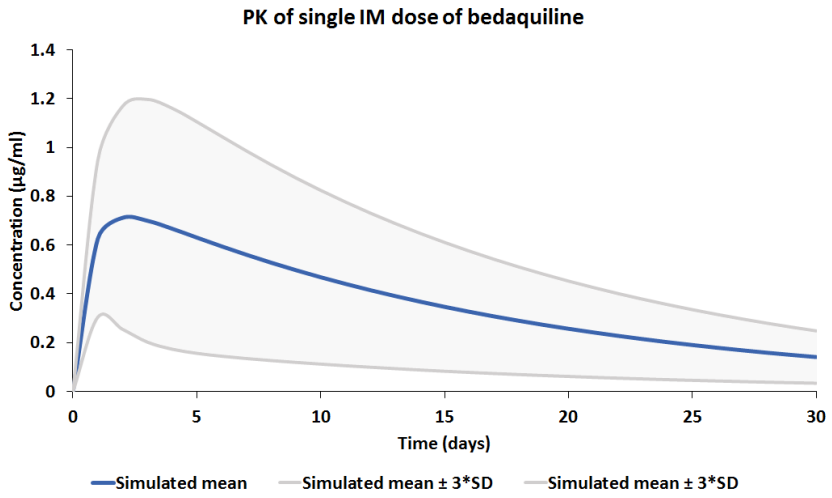


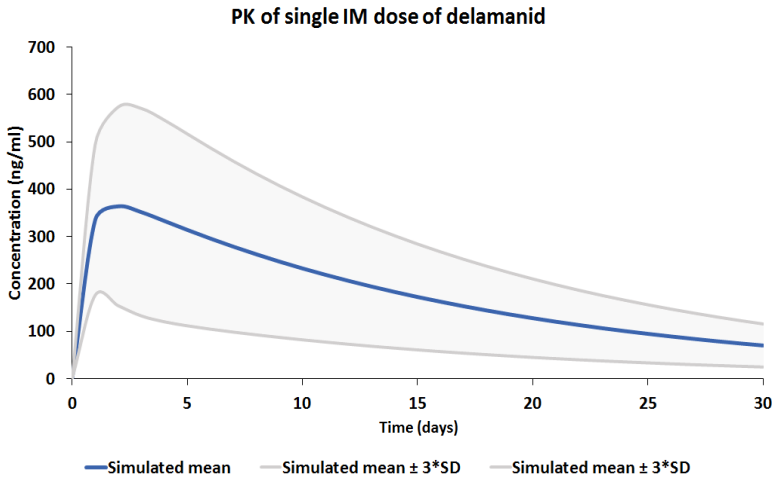


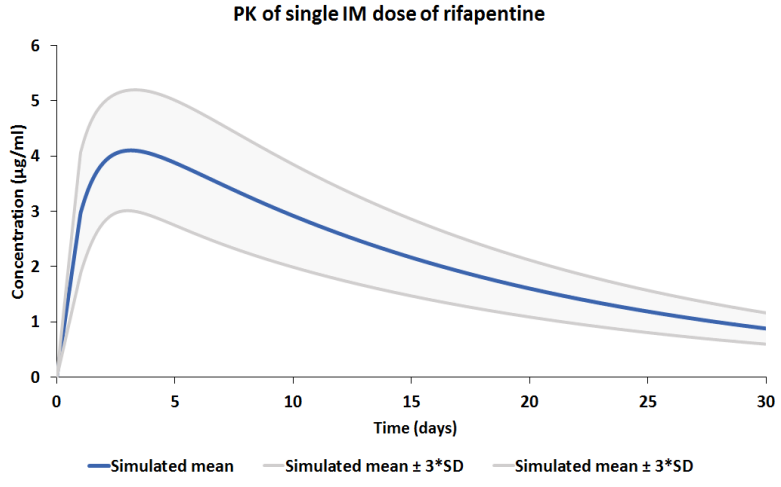
Simulation of long acting PK

IM Dose – 2000 mg/30 days IM release rate – 0.0025 h^{-1}

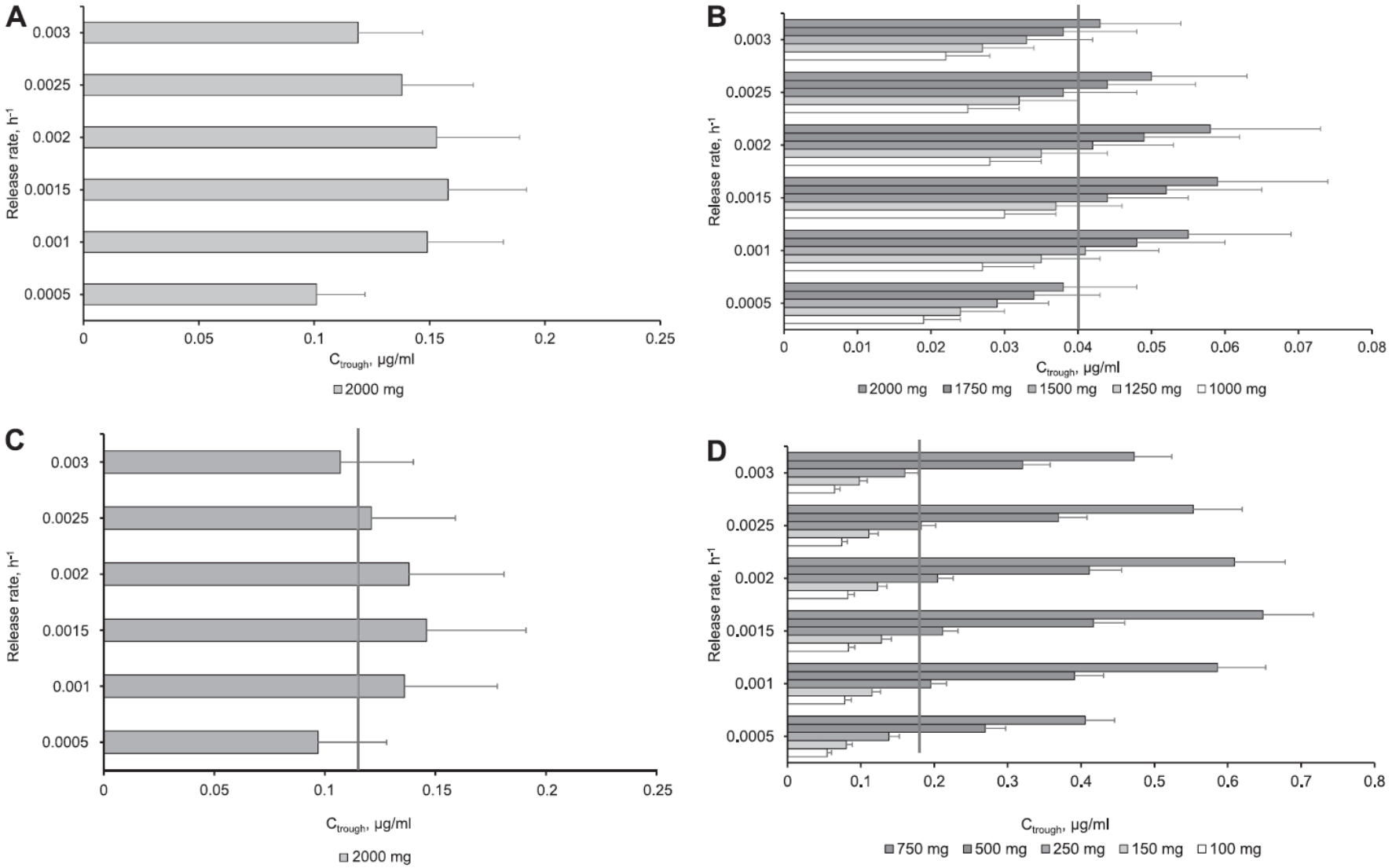
Drug	AUC (Mean ± SD) (µg.h/ml)	C_{max} (Mean ± SD) (µg/ml)	C_{trough} (Mean ± SD) (µg/ml)	Cut-off limit (µg/ml)
Bedaquiline	271 ± 65	0.72 ± 0.16	0.14 ± 0.04	1.6 (ECOFF)
Delamanid	89 ± 16	0.23 ± 0.04	0.05 ± 0.01	0.04 (ECOFF)
Rifapentine	1639 ± 160	4.12 ± 0.38	0.88 ± 0.09	0.06 (MIC)







Optimisation of dosing and formulation characteristics



A) bedaquiline **B)** delamanid **C)** isoniazid **D)** rifapentine

Translational pharmacokinetic modelling & simulation of an experimental long-acting injectable formulation of bedaquiline (BDQ - TMC207 - R207910)

An Vermeulen, Iwan Vervoort, Sophie Lachau-Durand, Ruud Leemans, Stefaan Rossenu, Koen Andries

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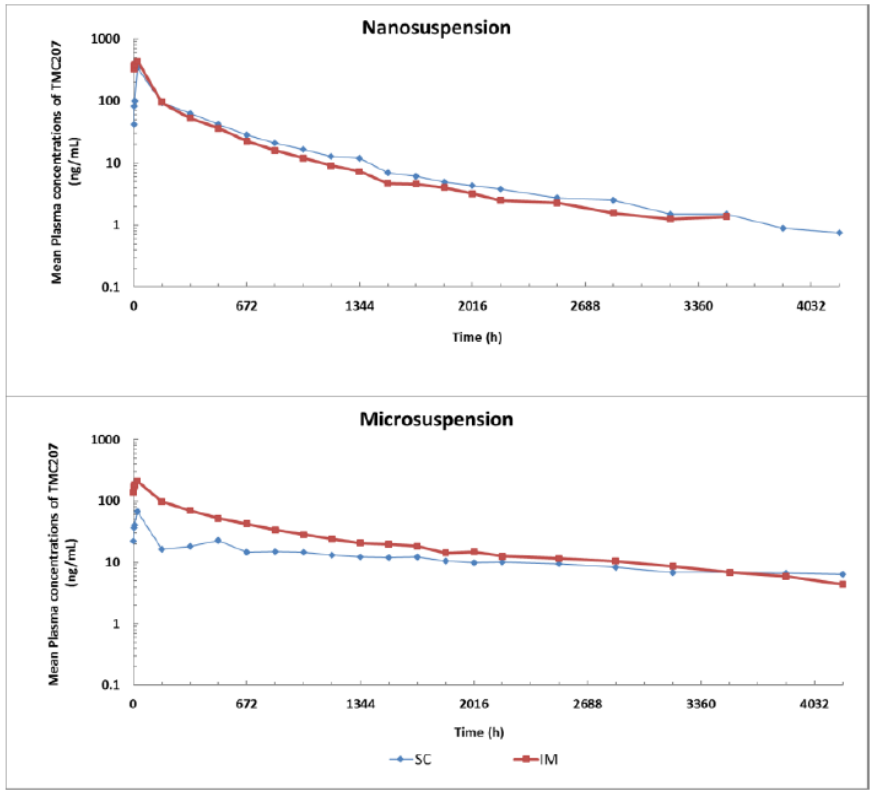
- Nano- or microsuspension particulate system in water
- Formulation concentration: 200 mg/mL
- Administration of nano- and microsuspension (SC and IM) at 80 and 160 mg/kg in mice (n=5/dose), and at 40 mg/kg in rats (n=3) and dogs (n=3)
- Follow-up for 3 (mice) or 6 months (rat, dog)

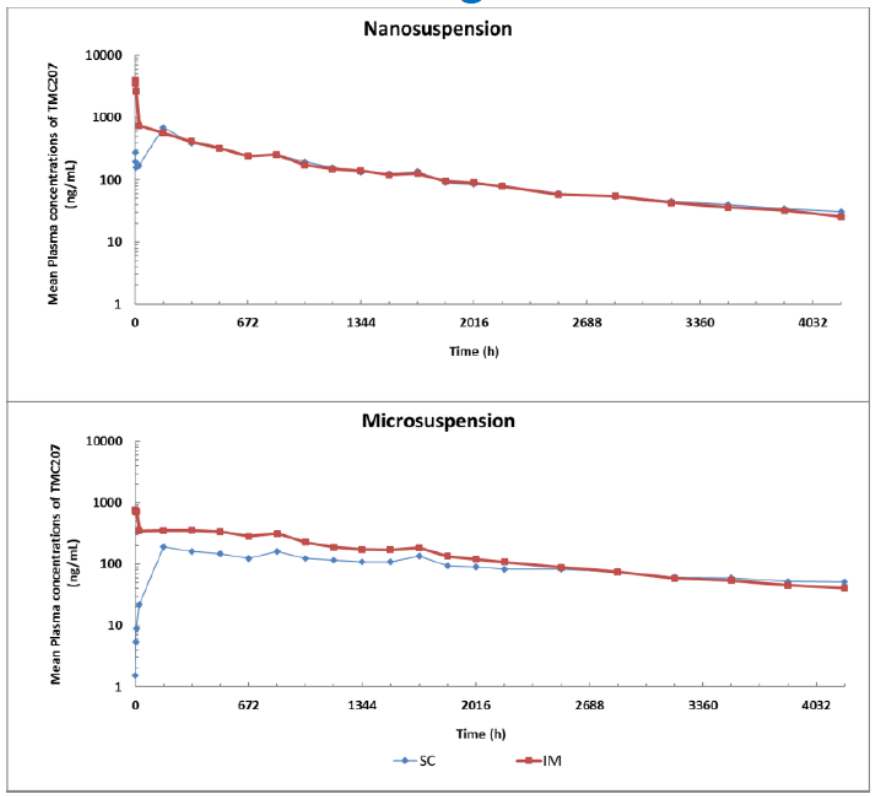
IM nano-/microsuspension data – SC/IM

Bedaquiline 40 mg/kg

Rat



Dog



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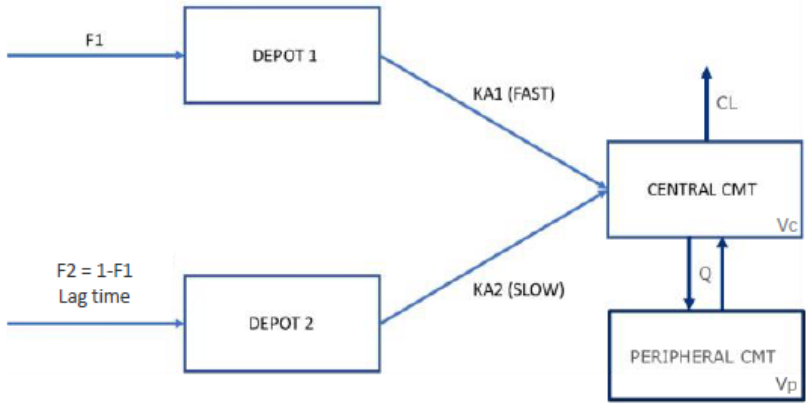
- Biphasic plasma concentration-time profile of BDQ
- **IM injection**
  - Peak plasma levels are reached earlier and are higher for the nano- than for the microsuspension
  - Apparent elimination half-life (flip-flop kinetics) is shorter for the nanosuspension (20-48 days) than for the microsuspension (30-56 days)
- **SC injection**
  - More gradual increase of BDQ's concentrations
  - Peak plasma levels and overall AUCs are lower (microsuspension), or similar (nanosuspension) compared to the IM administration route
- Plasma levels of the M2 metabolite decline in parallel with BDQ levels

PK parameters	Mouse	Rat	Dog
CL/F (mL/h/kg)	378	342	57.9
Vc/F (mL/kg)	42900	90800	2060
Q/F (mL/h/kg)	626	-	-
Vp/F (mL/kg)	42700	-	-
F1 (%) - fast	**54.2**	**42.7**	**4.01**
ka_1 (1/h) - fast	**0.73**	**1.42**	**9.83**
Lag time (h) - slow	**297**	**134**	**61.9**
F2 (%) - slow	**45.8**	**57.3**	**95.99**
ka_2 (1/h) - slow	**0.000797**	**0.000506**	**0.000596**
IIV (%CV)			
CL	34.4	8.71	15.6
Vc	47.6	16.1	30.6
ka	-	32.7	9.83
Residual error (%CV)	21.0	12.1	11.9



PopPK parameters obtained from patients' PO data:

CL/F, L/h	2.62 (2.49–2.75)
V/F, L/70 kg	198 (184–215)
Q1/F, L/h	3.66 (3.35–3.97)
VP1/F, L/70 kg	8,550 (7,940–9,230)
Q2/F, L/h	7.34 (6.8–7.84)
VP2/F, L/70 kg	2,690 (2,390–2,980)

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	AUC (µg.hr/mL)		Dose (gr)		
	Man (1 gr)	Mouse (480 mg/kg)	vs. AUC_{1mo} mouse	vs. AUC_{3mo} mouse	vs. AUC_{inf} mouse
1 month	188	870	4.64	6.94	7.93
3 months	333	1302	2.61	3.91	4.47
Infinity*	743	1488	1.17	1.75	2.00

* Large % extrapolated in man

- IM injection results in complete bioavailability of nano-/microsuspension formulations
- Peak levels are higher and apparent half-lives shorter for nano- as compared to microsuspensions
- Microsuspensions show sustained plasma levels over a period of 1 month
- The candidate LAI formulations hold promise for further development

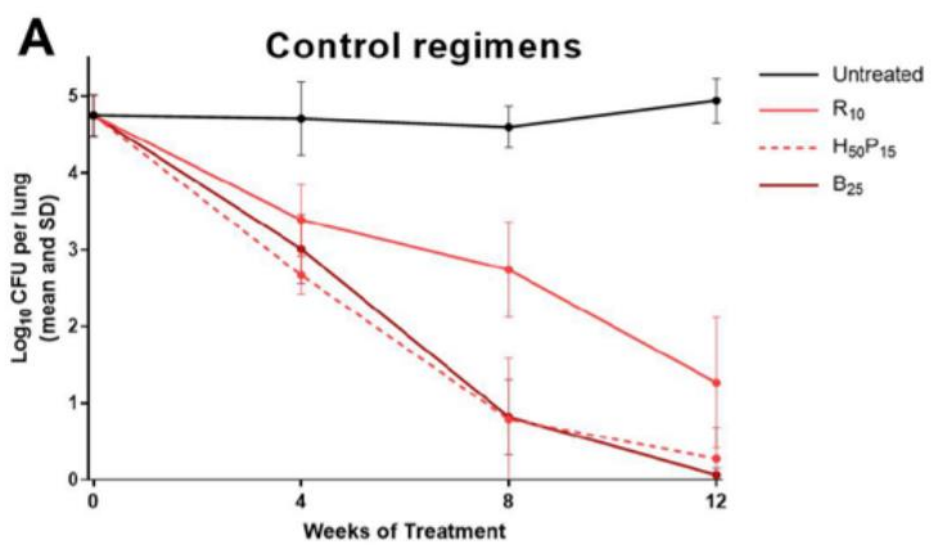
Activity of a Long-Acting Injectable Bedaquiline Formulation in a Paucibacillary Mouse Model of Latent Tuberculosis Infection

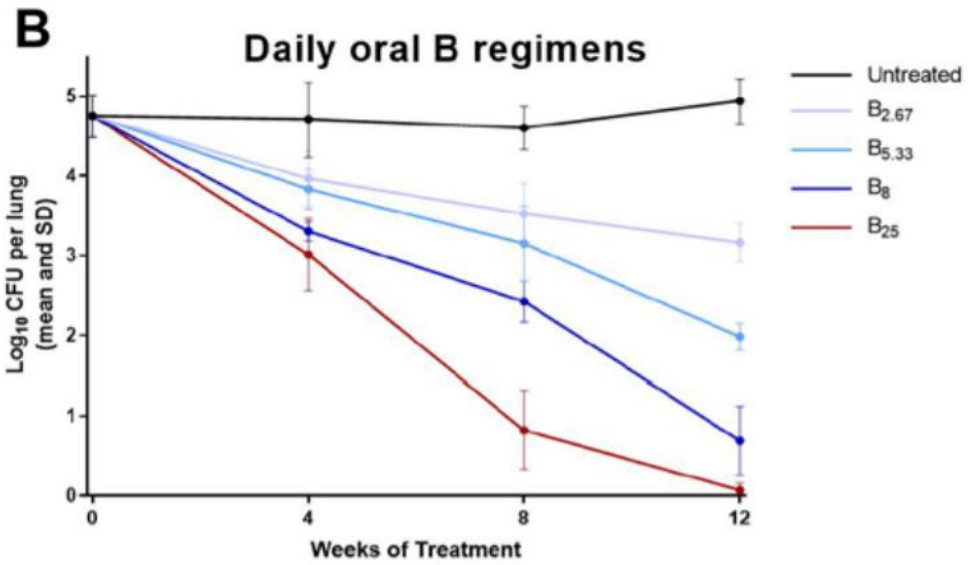
Amit Kaushik,[a] Nicole C. Ammerman,[a] Sandeep Tyagi,[a] Vikram Saini,[a]* Iwan Vervoort,[b] Sophie Lachau-Durand,[b] Eric Nuermberger,[a] Koen Andries[b]

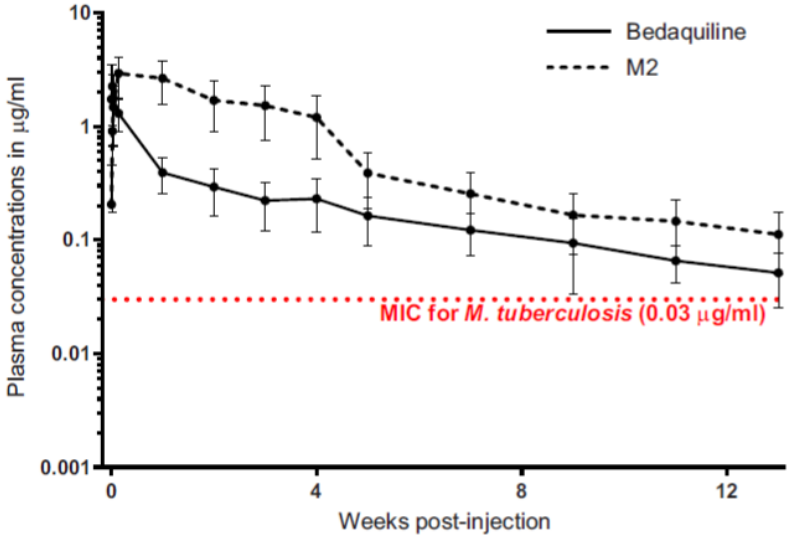
[a]Center for Tuberculosis Research, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
[b]Janssen R&D, Beerse, Belgium

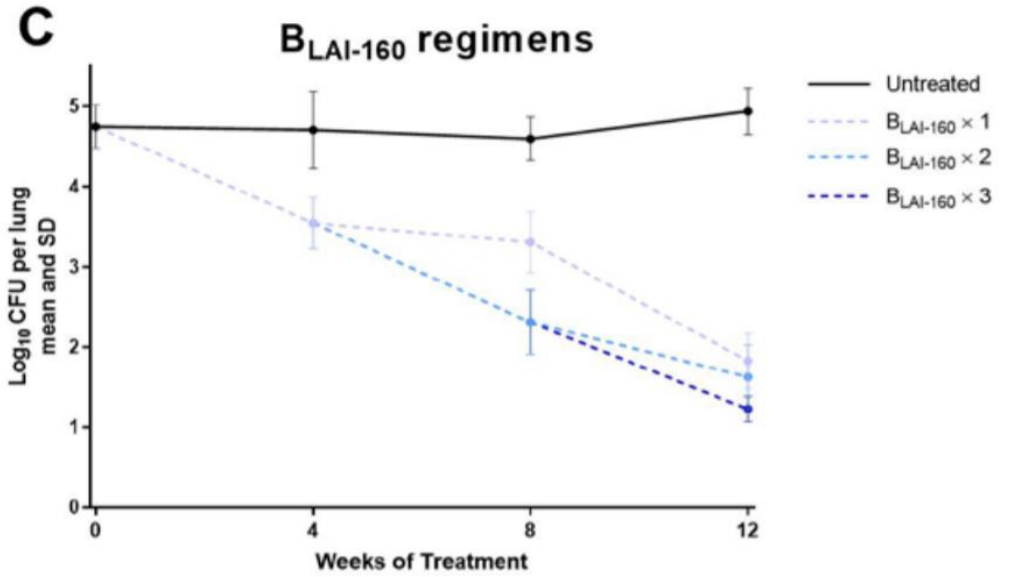
AIM: to describe the PK and activity of an LAI bedaquiline formulation in the validated paucibacillary mouse model of LTBI and comparison with other oral regiments

Regimes	Total bedaquiline dose (mg/kg) administered in 12 wk	Regimen description
Untreated	NA	Negative control, no drug administered
R_{10} (5/7)	NA	Positive control, rifampin (R) at 10 mg/kg administered dailya by gavage
$H_{50}P_{15}$ (1/7)	NA	Positive control, isoniazid (H) at 50 mg/kg and rifapentine (P) at 15 mg/kg administered once weekly by gavageb
B_{25} (5/7)	1,500	Positive control, bedaquiline at 25 mg/kg administered daily by gavage
B_{8} (5/7)	480	Bedaquiline at 8 mg/kg administered daily by gavage
$B_{5.33}$ (5/7)	320	Bedaquiline at 5.33 mg/kg administered daily by gavage
$B_{2.67}$ (5/7)	160	Bedaquiline at 2.67 mg/kg administered daily by gavage
$B_{LAI\text{-}160}$ (1/28) × 3	480	Long-acting injectable bedaquiline formulation (BLAI) at 160 mg/kg administered every 28
$B_{LAI\text{-}160}$ (1/28) × 2	320	BLAI at 160 mg/kg administered every 28 days by intramuscular injection for two total doses: day 0 and day 28 (wk 4)
$B_{LAI\text{-}160}$ (1/28) × 1	160	BLAI at 160 mg/kg administered once on day 0


A
Control regimens
Untreated
R10
H50P15
B25
Log10 CFU per lung (mean and SD)
Weeks of Treatment


B
Daily oral B regimens
Untreated
B2.67
B5.33
B8
B25
Log10 CFU per lung (mean and SD)
Weeks of Treatment


Bedaquiline
M2
MIC for M. tuberculosis (0.03 μg/ml)
Plasma concentrations in μg/ml
Weeks post-injection


C
BLAI-160 regimens
Untreated
BLAI-160 × 1
BLAI-160 × 2
BLAI-160 × 3
Log10 CFU per lung mean and SD
Weeks of Treatment

Conclusions

- One, two, and three doses of BLAI-160 resulted in decreases of 2.9, 3.2, and 3.5 $\log_{10}$ CFU/lung, respectively, by week 12.
- Daily oral dosing with B2.67, B5.33, and B8 decreased lung CFU counts by 1.6, 2.8, and 4.1 $\log_{10}$, respectively.
- One dose of BLAI-160 exhibited activity for at least 12 weeks.
- The sustained activity of BLAI-160 indicates that it shows promise as a short-course LTBI to ensure treatment completion.
- The present results further support bedaquiline-based regimens for LTBI treatment in contacts of patients with MDR-TB, and LAI formulations in particular could significantly simplify what could be an otherwise long and complicated treatment.

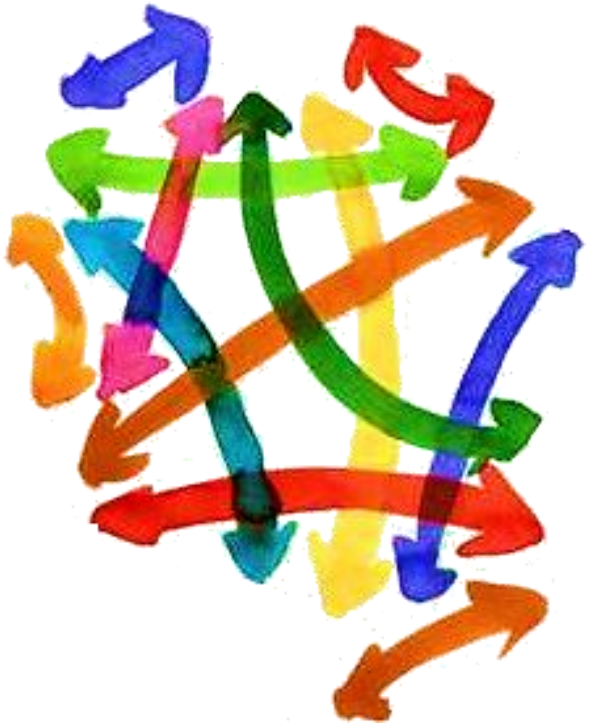
Development and optimisation of LA formulation is a multifactorial process

Synthesis

Cost
Scalability
Sterility
Compatibility with drug candidate

Drug(s)

Pharmacokinetics
Combination
Adverse drug reaction
Drug-drug interactions



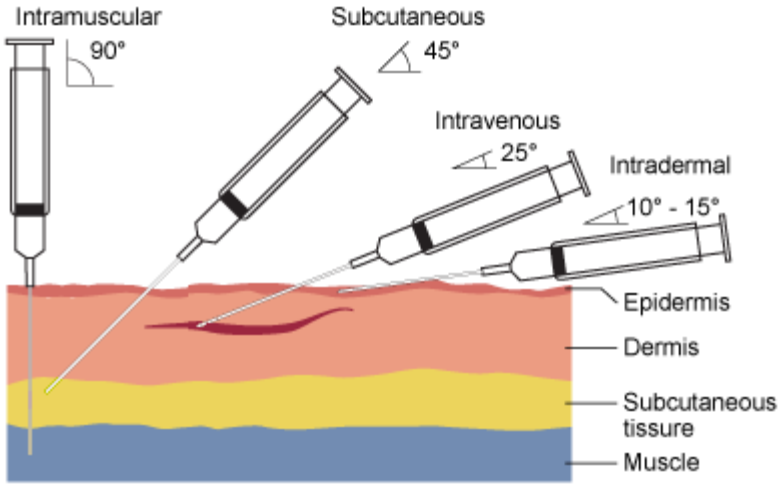
Formulation/Device

Loading
Injection volume
Adverse drug reaction
Duration of release
Tuneability
Consistency

Other factors

Compatibility with healthcare system
Patient acceptability

Technological platforms currently explored across multiple disease areas

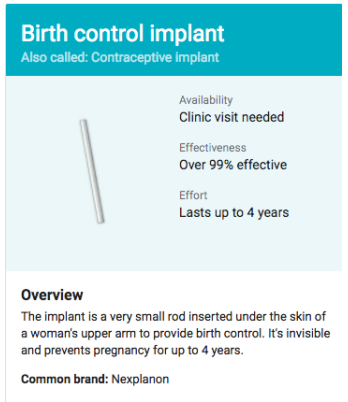


Interval = weeks to years
Max dose = 1500mg (multiple injections)
Administration = SC - No supervision required.
IM - Under supervision

Microneedle patches

Interval = week to month
Max dose = 500mg
Administration = No supervision required – pain free

Implants



Interval = months to years
Max dose = 200mg
Administration = Under supervision

Opportunities and limitations

Potential advantages	Potential disadvantage
Inter-individual variability	Large injection volume
Total dose reduction	Challenges in combining agents
Avoidance of GI adverse reaction	Requirement for oral lead-in
Decrease magnitude of DDIs	Management of adverse effects and DDIs
Improved adherence	Resistance consequences of missed doses
Compatibility with DOT	Tail PK
Decrease cost	Limited compatibility with the formulations

TB and HIV co-infection

- TB is the leading cause of death in HIV-infected persons worldwide, and this has persisted despite the fact that provision of antiretroviral therapy (ART) is increasing
- Majority of co-infected patients with HIV and TB received ART.
- HIV-infected persons account for 12% of people who develop TB annually, and 25% of deaths from TB.

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One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis

S. Swindells, R. Ramchandani, A. Gupta, C.A. Benson, J. Leon-Cruz, N. Mwelase, M.A. Jean Juste, J.R. Lama, J. Valencia, A. Omoz-Oarhe, K. Supparatpinyo, G. Masheto, L. Mohapi, R.O. da Silva Escada, S. Mawlana, P. Banda, P. Severe, J. Hakim, C. Kanyama, D. Langat, L. Moran, J. Andersen, C.V. Fletcher, E. Nuermberger, and R.E. Chaisson, for the BRIEF TB/A5279 Study Team*

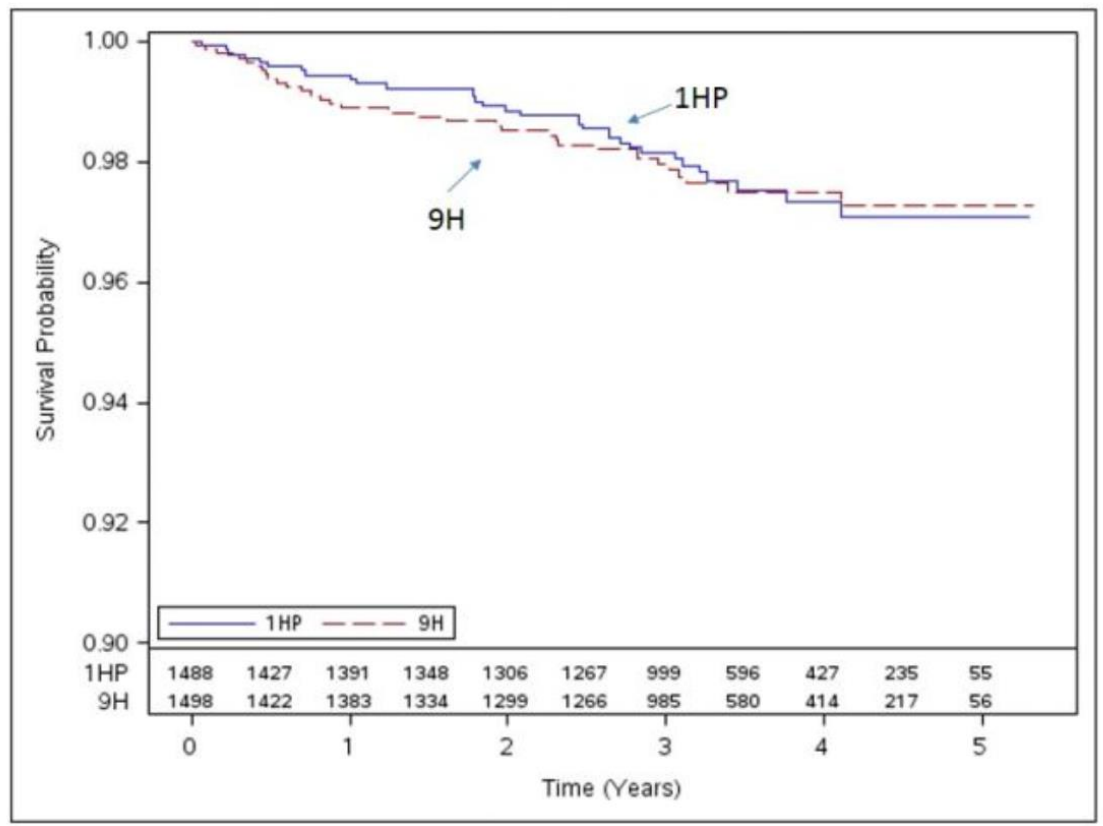
Hypothesis:

Four weeks of daily rifapentine and isoniazid will be non-inferior to nine months of isoniazid for preventing TB in people with HIV infection

Primary Objective:

To compare the efficacy of a 4-week daily regimen of rifapentine and isoniazid (1HP) with a 9-month daily regimen of isoniazid (9H) for the prevention of TB in adults and adolescents with HIV infection

Time to endpoint



2019 Global New TB Drug Pipeline [1]

Discovery | **Preclinical Development** | **Clinical Development**

Lead Optimization → **Early Stage Development** → **GMP/ GLP Tox.** → **Phase 1** → **Phase 2** → **Phase 3**

Diarylthiazoles

DprE1 Inhibitors

Direct InhA Inhibitors

Mtb energy metabolism

Macrolides

Mycobacterial Gyrase Inhibitors

Arylsulfonamides

Inhibitors of MmpL3, Translocase-1, Clp, PKS13

Oxazolidinones

Squaramides

CPZEN-45*

Spectinamide - 1810*

TB-47*

TBAJ-587

TBAJ-876

GSK-286*

Sanfetrinem

S-004992*

SPR720*

TBI-223

BTZ-043*

TBI-166

Macozinone* (PBTZ-169)

GSK-656* (070)

TBA-7371*

Contezolid

OPC-167832*

Telacebec* (Q203)

Delpazolid (LCB01-0371)

Sutezolid

SQ-109*

Macozinone*

Bedaquiline* (TMC-207)

Delamanid* (OPC-67683)

Pretomanid* (PA-824)

*New chemical class. Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound series identified: http://www.newtbdrugs.org/pipeline/discovery

Underline = new to Phase since Oct 2018

WORKING GROUP ON NEW TB DRUGS

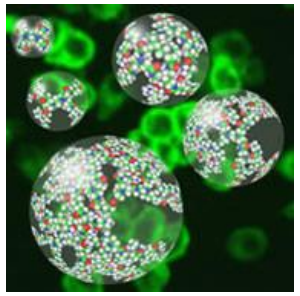
www.newtbdrugs.org

Updated: March 2019

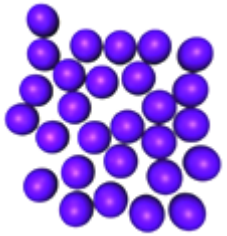
Use of nanobiomaterials to enhance drug delivery

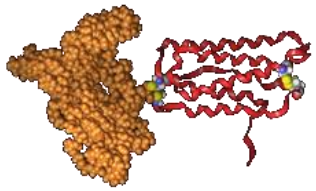
PASSIVE

NANOEMULSION

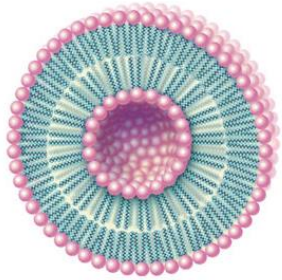


NANOSUSPENSION





BIO-POLYMERS



LIPOSOME

SOLUBILITY

BIOAVAILABILITY

EPR EFFECT

SUISTAINED RELEASE

ACTIVE

SMALL LIGANDS

PROTEINS

PEPTIDES

ANTIBODIES

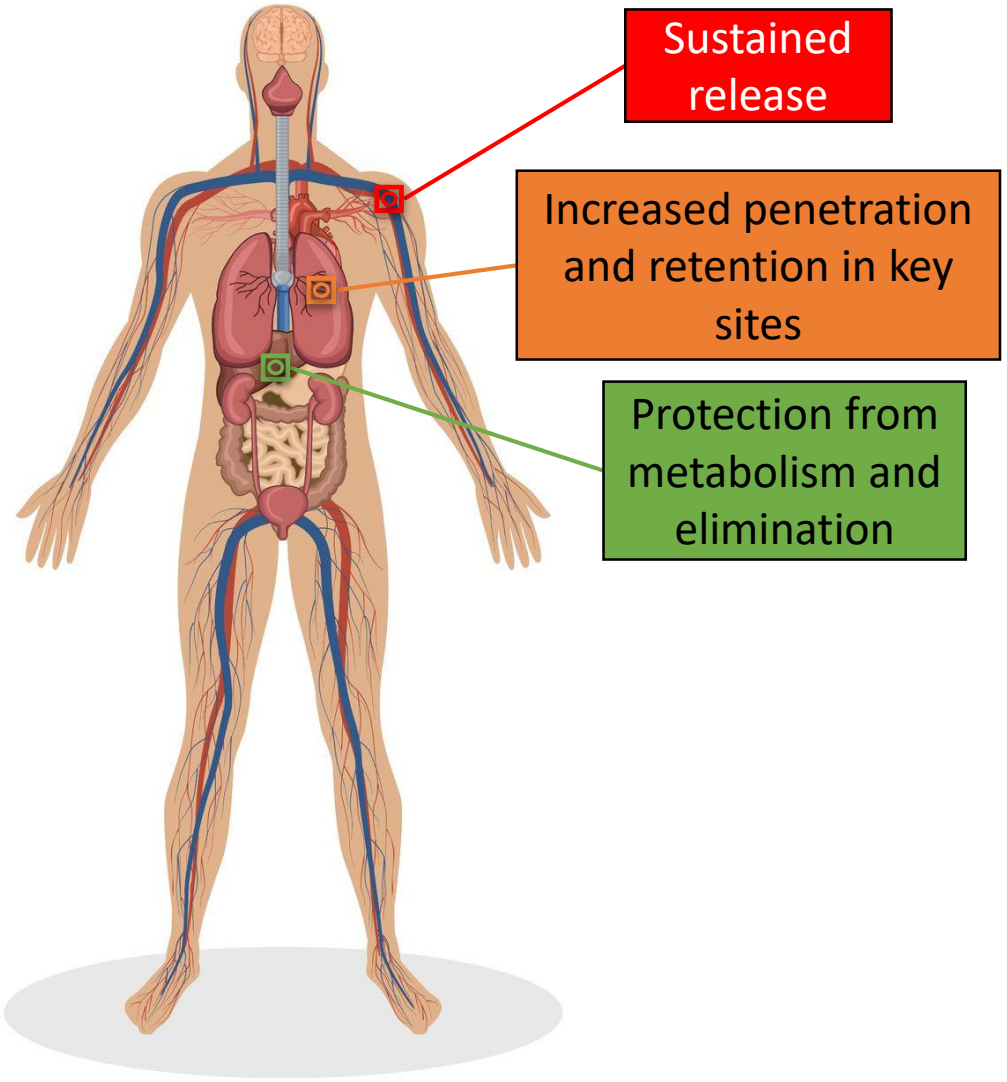
NUCLEIC ACIDS

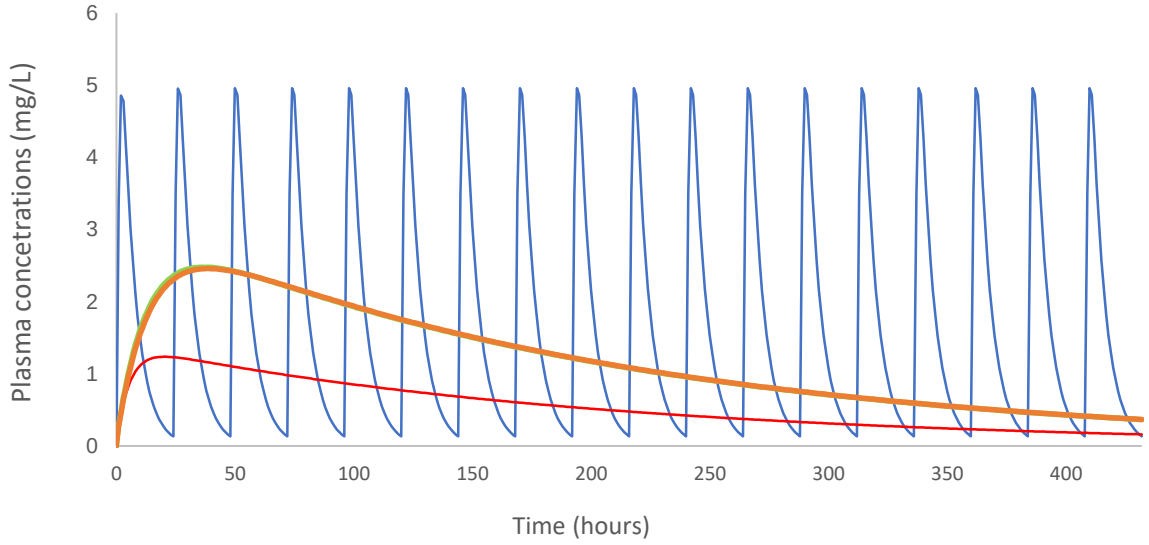
TISSUE TARGETING

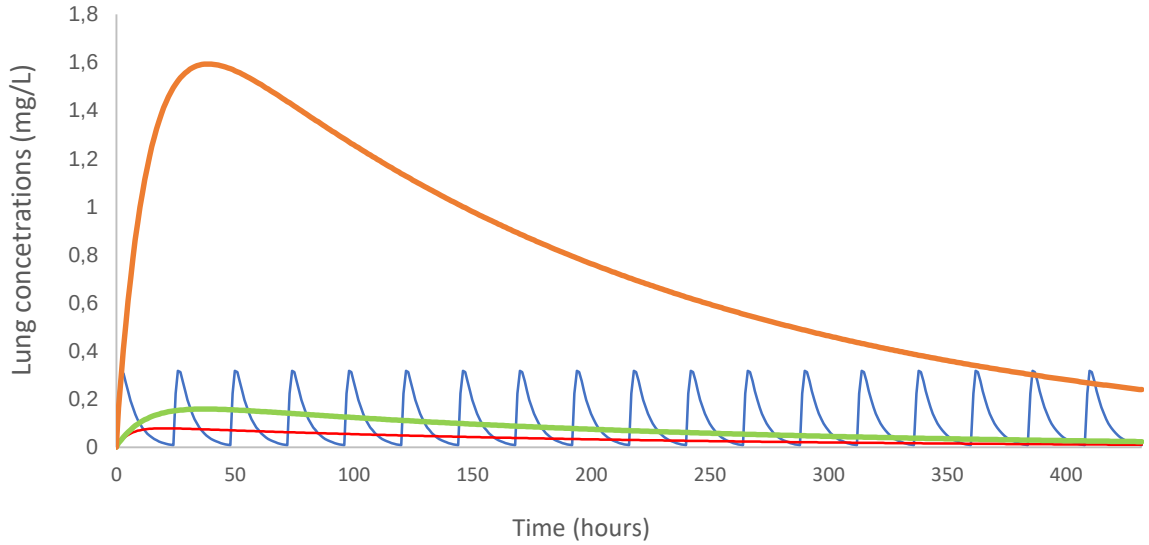
PATHOGEN TARGETING

TUMOR TARGETING

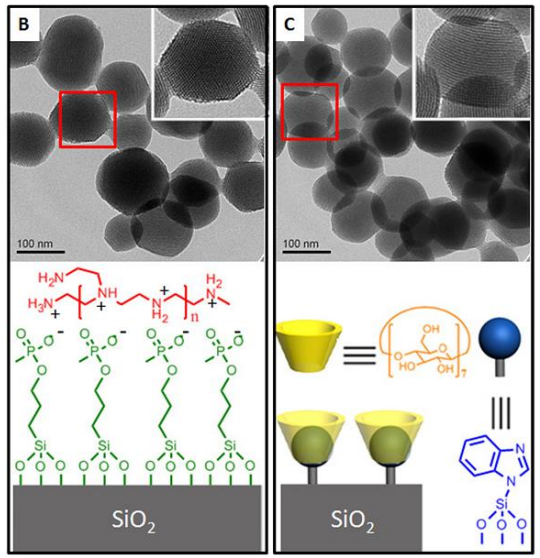
Use of nanobiomaterials to enhance drug delivery

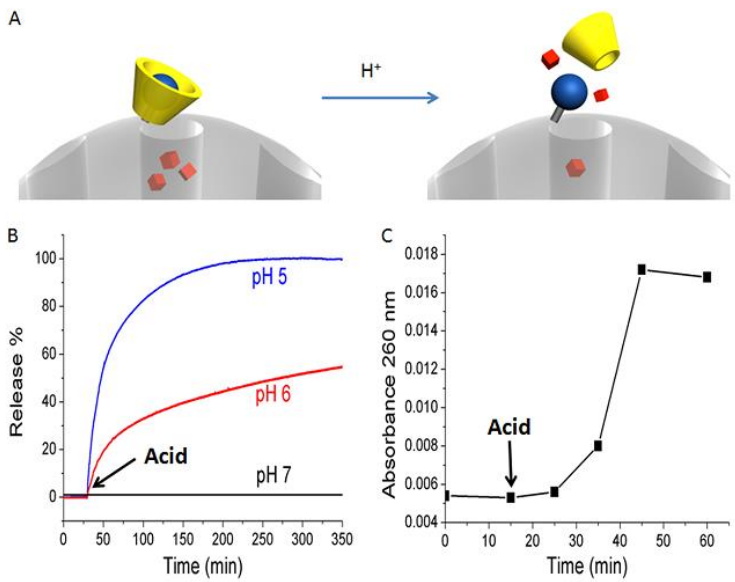






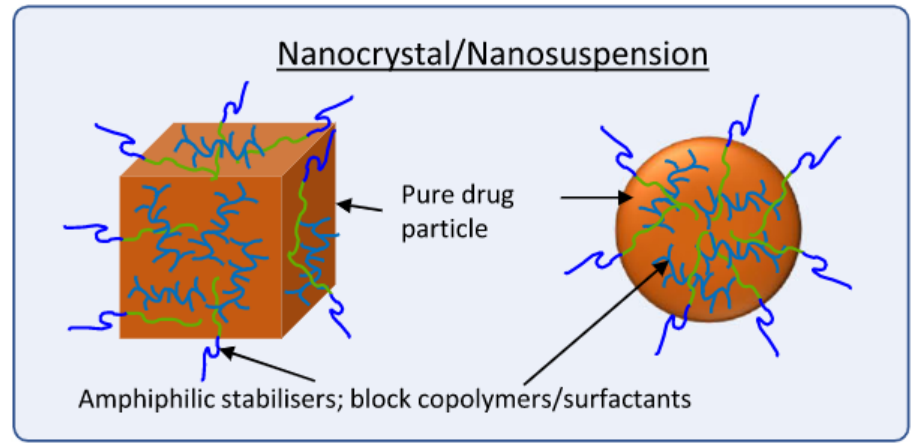
Targeted Intracellular Delivery of Antituberculosis Drugs to *Mycobacterium tuberculosis*-Infected Macrophages via Functionalized Mesoporous Silica Nanoparticles

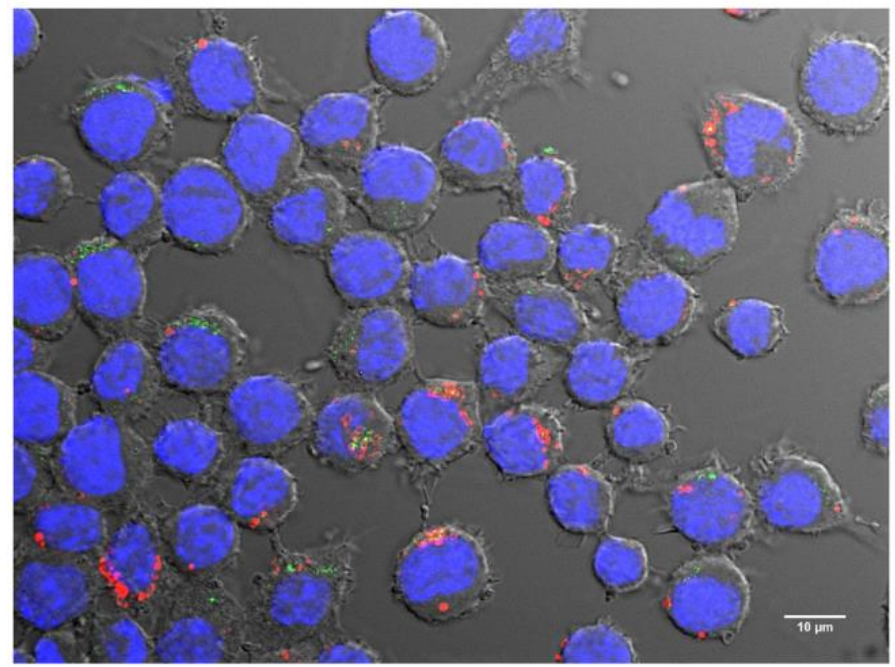




Nanomedicines towards targeting intracellular *Mtb* for the treatment of tuberculosis

Samantha Donnellan[1*] & Marco Giardiello[2]

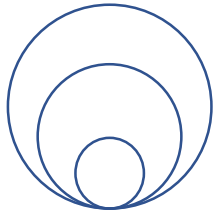




Posology, pharmacokinetic and pharmacodynamic characteristics of LAIs – choice of agent

Liverpool 2017-2020
Apps = 92 goal = 64

Torino 2003-2005
Apps = 21 goal = 1



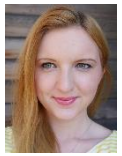
Therapeutic concentrations

Future perspectives

- The potential for a “one shot cure” is an irresistible ambition for future TB treatment, considering compatibility with directly observed therapy (DOT)
- The development of LA products is complex and challenging and thus far, all successful LA agents are administered separately.
- Management of adverse effects may be more challenging with LA injectable formulations as they cannot be immediately discontinued.
- New LA/ER formulations are likely to have their most immediate impact on the treatment of LTBI
- Coupled with a field-friendly diagnostic test an LA/ER TB formulation could enable a test-and-treat strategy that would greatly increase the possibility of TB eradication.

Acknowledgements

Rajith Kumar Reddy
PBPK for LA and novel formulations



Alice Howarth
DMPK of nanobiomaterials

Hannah Kinvig
Transporter mediated DDIs and PK in elderly

Fazila Bunglawala
QSAR and PBPK for neonates

Nicolas Cottura
PBPK for LA and novel formulations

Adam Wood
DMPK of nanobiomaterials and PK modelling in special populations

Sandra Granana
DMPK of Complex DDIs

Doaa Ahmed Mohamed
Computational modelling of NPs

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Saye Khoo

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Justin Chiong
Lee Tatham
Megan Neary
Helen Box
Qurat Shabir

Steve Rannard
Tom McDonald
Marco Giardiello
Chris David
James Hobson
Neill Barry

REFINE leap PKTK pharmacokinetics toxicokinetics

NIH National Institutes of Health

European Commission

USAID FROM THE AMERICAN PEOPLE

EPSRC Engineering and Physical Sciences Research Council

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