Pharmacokinetics of bedaquiline in sputa from a Haitian MDR/RR-TB cohort

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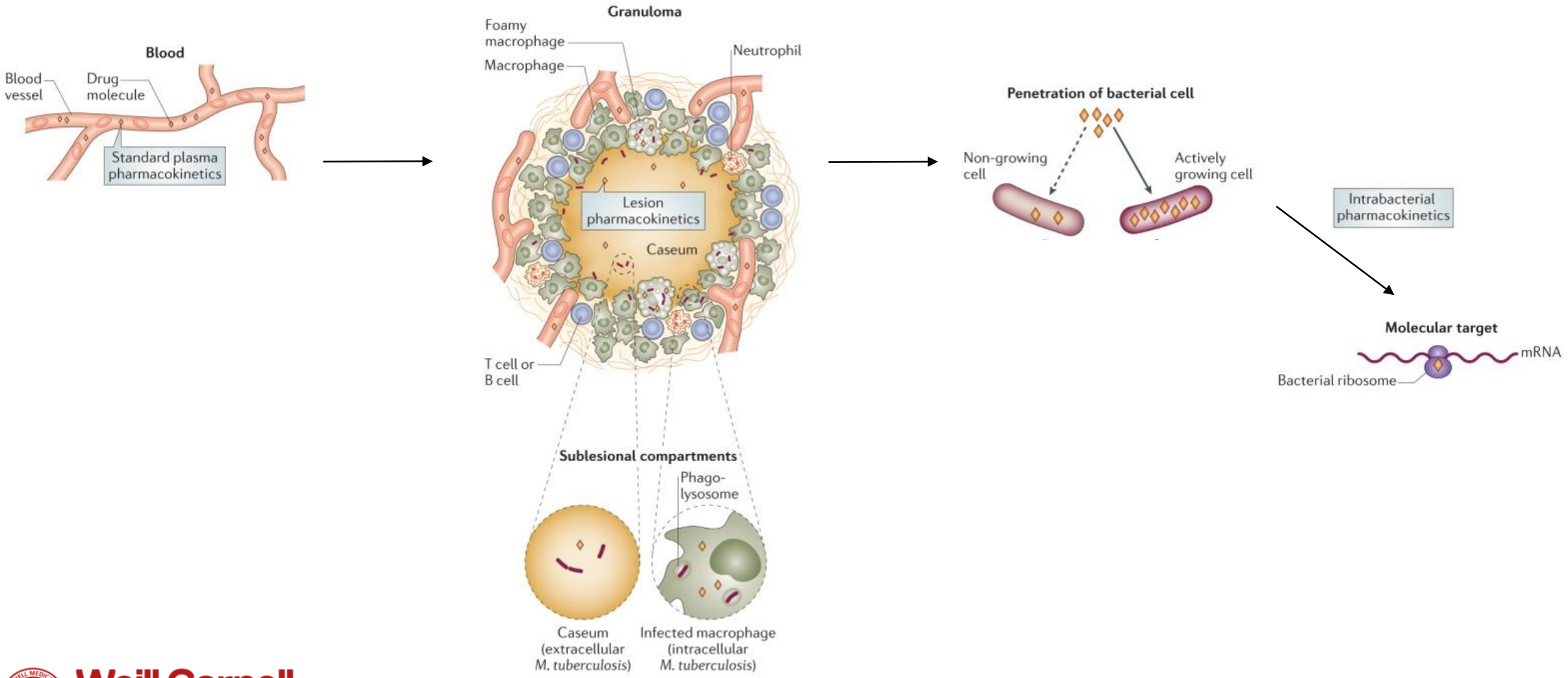
Pharmacokinetics at site of disease



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Dartois, *Nature Reviews* 2014

Study Design

- Observational study of 24 adults with pulmonary MDR/RR-TB treated at GHESKIO, Port-au-Prince, Haiti 2019 – 2022 with an objective of testing second-line drug levels in sputa

- Participants were enrolled prior to taking second-line medications

- Treatment regimen for all participants:
  - bedaquiline 400mg daily x 2 weeks then 200mg TIW x 22 weeks
  - levofloxacin 10-15mg/kg daily
  - linezolid 600mg daily for 12 months
  - clofazimine 100mg daily
  - pyrazinamide 15mg/kg daily

Schedule of specimen collection																
	Enroll	Week	Month													
		2	1	2	3	4	5	6	7	8	9	12	15	18	19	20	21
Sputum collection with Mtb isolate preservation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Plasma for PK studies		X															
Sputum for PK studies		X															

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Table 1. Description of 24 adults with MDR/RR-TB in Haiti	
Age, median [IQR]	32 [27, 43]
Sex, n (%)	
Female	11 (46)
Male	13 (54)
Weight at diagnosis (kg), median [IQR]	49.9 [43.3, 53,4]
Baseline creatinine (mg/dL), median [IQR]	0.65 [0.55, 0.7]
Baseline hemoglobin (g/dL), median [IQR]	10.8 [10.0, 11.8]
People living with HIV, n (%)	4 (17)
History of previous first-line TB treatment, n (%)	
Yes	20 (83)
No	4 (17)
Presence of cavities on diagnostic chest xray, n (%)	
Yes	10 (42)
No	14 (58)
Treatment outcome, n (%)	
Cure	21 (88)
Treatment completion	1 (4)
On treatment*	1 (4)
Lost to follow-up	1 (4)
*Participant left care after one month, eventually re-engaged and is on-treatment.	

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Table 2. Sputum and plasma drug concentrations, 2 weeks after starting treatment			
Drug	Sample type, 4 hours after drug administration	Median [IQR]	Sputum:plasma ratio (median, [IQR])
Bedaquiline (ng/g)	sputum	81.1 [32.4, 332]	**0.06** [0.02, 0.18]
	plasma	2340 [1300, 3015]	
Bedaquiline metabolite (M2) (ng/g)	sputum	98.2 [59.1, 1050]	0.19 [0.12, 1.48]
	plasma	545 [462, 839]	
Levofloxacin (ng/g)	sputum	10,030 [6880; 12,300]	**1.01** [0.73, 1.29]
	plasma	9775 [8775; 10,200]	
Linezolid (ng/g)	sputum	9915 [8210; 12,300]	0.89 [0.78, 1.14]
	plasma	10,950 [9335; 13,000]	
Clofazimine (ng/g)	sputum	9.98 [5.8, 65.5]	0.04 [0.03, 0.32]
	plasma	246 [186, 321]	
Pyrazinamide (ng/g)	sputum	29,700 [23,800; 35,300]	0.81 [0.69, 1.01]
	plasma	37,150 [32,300; 39,250]	

Preliminary Conclusions

- There may be periods at the beginning and end of treatment when there is de facto monotherapy, creating the opportunity for resistance.

- We need better methods to assess drug pharmacokinetics at the site of disease during drug development.

Next steps

- Testing the stored serial Mtb culture isolates from this study for known mutations associated with drug resistance

- Checking drug levels in sputa at later time points on treatment and following the end of treatment

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