The need for an increased pipeline
Updates from the field

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Ernst Ludwig Kirchner. Blick auf Davos. 1924. Bündner Kunstmuseum Chur, Switzerland
The Magic Mountain

- Sunlight
- Nutrition
- Supine
Ferrari 156 Sharknose
1961
- Vaccines
- Diagnostics
- Treatments

1800s:
- Improved socioeconomic conditions

1882: M tbc discovered

1895: X-rays discovered

1920: BCG

1944 - 1961 TB DRUGS
HIV negative cases with active TB

Pre-chemotherapy era:
- 10-year fatality rate 70%

XDR TB Western Cape:
- 3-year fatality rate 60%

Cape Town:
• >20,000 TB cases pa, 10% children <8y
• HIV prevalence in TB cases: 51%
• MDR >1,500/year, XDR >100/year
• Cost of drug resistance >50% of TB budget

WHO:
• XDR-TB in >50 countries
• >75% resistant TB in previously untreated patients
Drug resistance and poor compliance

Hollow Fiber Model

Gumbo et al JID 2007:195;194-201
Srivastava et al JID 2011:204; 1951-9
• Does non-compliance cause multidrug-resistant TB?
  – Fast and slow growing bacteria
  – 0.5% INH-resistant, 0.5% RIF-resistant
  – HRZ at human serum levels
  – Poor compliance patterns as seen in practice

• Augmentation of resistance?
Does non-compliance cause multidrug-resistant TB?
- Fast and slow growing bacteria
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- No increase in % resistance, no MDR TB
Underestimating the enemy

• Variability within a patient
  – Cavity walls, fibrosis
  – Bacterial subpopulations

• Between patient variability
  – Drug levels
  – Resistance levels
Innovation (at once, if not sooner)
Ferrari F1 - 1950 to 2013
continuous process of innovation and testing
(and failures too)
TB Drug Development

• Pathway for evaluation
  1. Mouse model
  2. 14-day EBA
  3. 8-week study
  4. Registration trial in MDR or DS TB
28 June 2005
First TMC207 dose to a TB patient
Proof of concept - activity

C202: TMC207 7-day EBA

Log Fall (cfu/mL)

Day

0 1 2 3 4 5 6 7 8

TMC207 25 mg
TMC207 100 mg
TMC207 400 mg
RIFAMPICIN 600 mg
ISONIAZID 300 mg

TMC207 400mg for 8 weeks

MDR regimen + placebo vs MDR regimen + TMC207
Sustained culture conversion in liquid media, n=44

p = 0.003

8.7% culture negative
47.5% culture negative

TMC207 400mg for 24 weeks

MDR regimen + placebo vs MDR regimen + TMC207
Sustained culture conversion in liquid media, n=132

Difference in time to conversion: p = <0.001
Time to 50% conversion: 12 weeks vs 18 weeks

Source: Janssen Research & Development
3 Dec 2012 (7y, 5m, 5d later)
Experts at FDA hearing vote pro registration
The Magic Bullet

• 3 drugs from new classes
  – No resistance
  – All forms of TB
H, R, Z, E, S
AG, FQ, 2\textsuperscript{nd} lines
PA, BDQ, DEL
LIN, β-lactams, CLO

Antiretroviral agents
Low market potential
Limited trial capacity
Urgency
Never discourage anyone who continually makes progress, no matter how slow.

Plato 428 – 348 BC