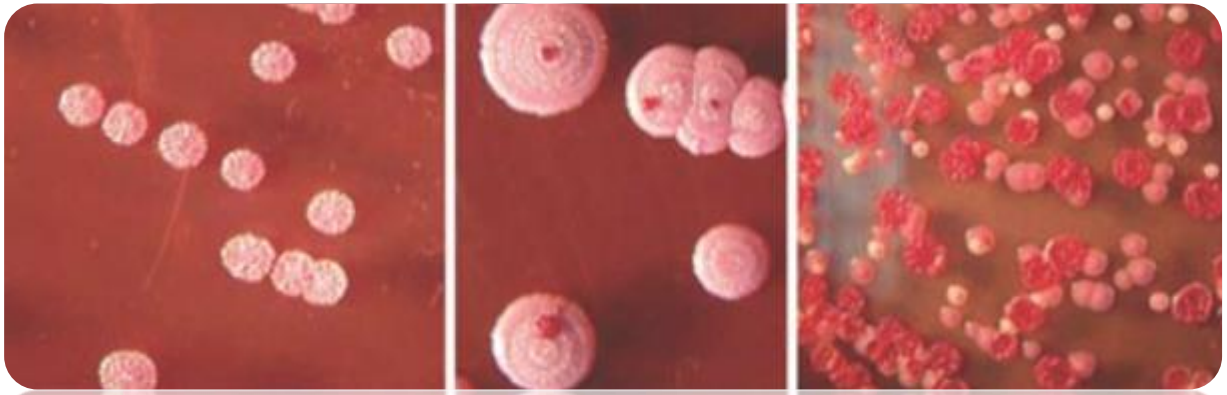


Novel treatment opportunities for acute melioidosis and other infections caused by intracellular pathogens

Jutta Heim, PhD

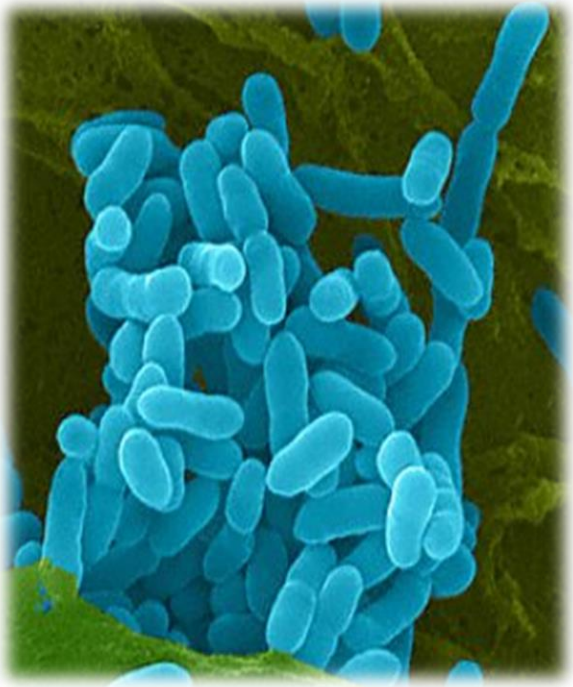
Senior Advisor and Director of the Board of Evolva S/A and of Nuevolution S/A

The Proposal

- Identify and develop a quick, cheap and reliable diagnostic kit for detection of *Burkholderia pseudomallei*
  - Follow identified leads from BARDA
- Identify and bring to patients an oral, affordable treatment option for the acute and the persister (eradication) phase of melioidosis
  - Based on marketed or close-to-market antibiotics
  - Possibly reformulated
  - Possibly as drug combination
- Evaluate Bp leads against other Gram-negative intracellular pathogens
  - Francisella, Coxiella, Legionella and more…

Burkholderia pseudomallei, the Bad Bug

- Recently renamed from *Pseudomonas* to *Burkholderia*
- Causative agent of melioidosis
- Closest neigbour *B. mallei*, causative agent of glanders
- Gram-negative rod, residing inside phagocytes (macrophages)
- Very high infectivity (10 CFU!)
- CDC Category B Select Agent

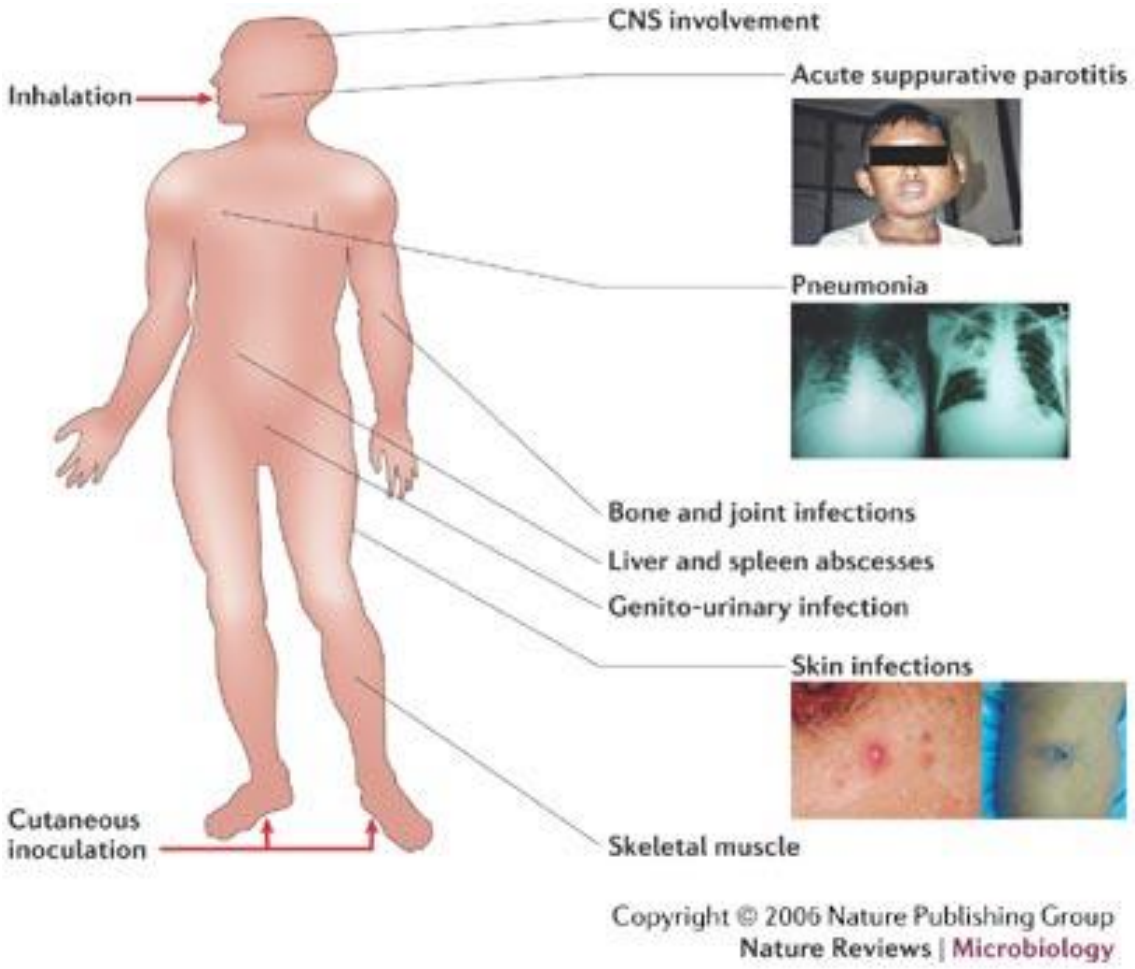


B. pseudomallei

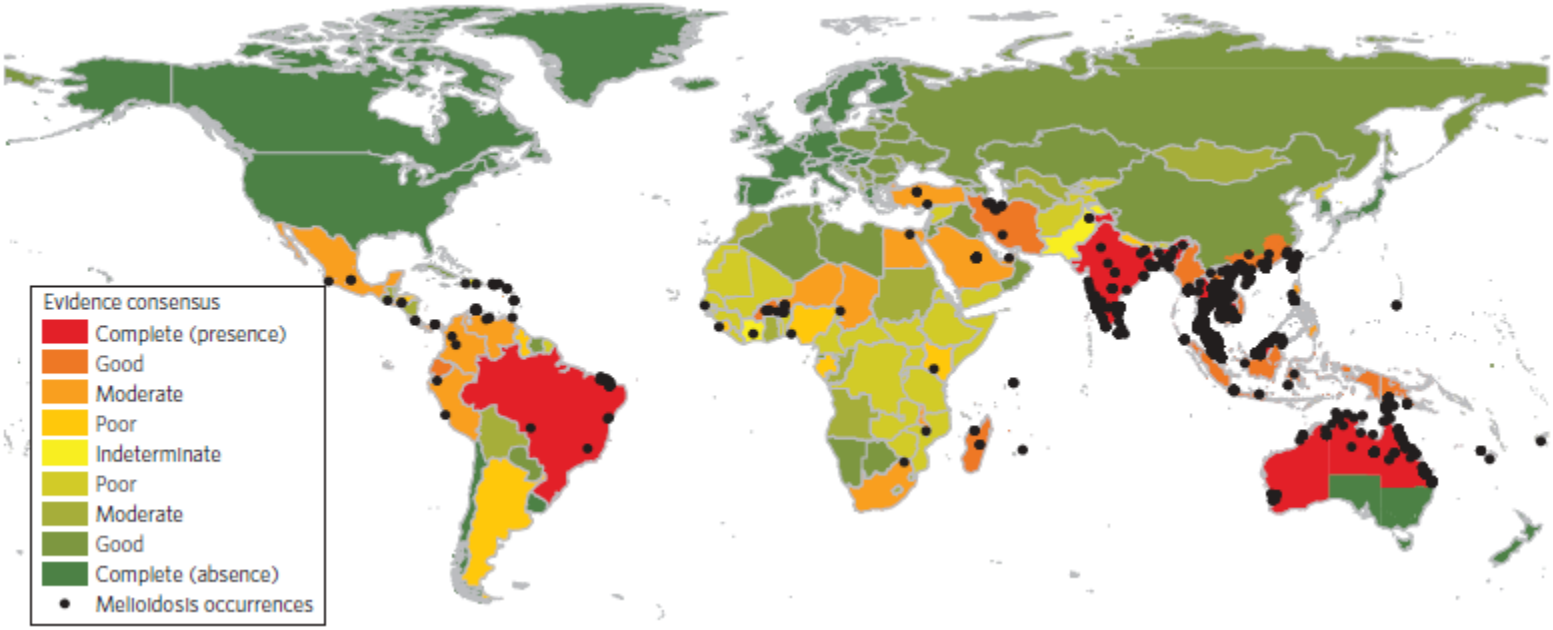
Dennis Kunkel Microscopy 2004

Melioidosis, a Disease with Many Faces

- Mortality rate 20-50% (depending on onset of treatment and geography)
- Comorbidity Diabetes
  - Localised
  - Pulmonary
  - Bloodstream or
  - Disseminated infection



Epidemiology of Melioidosis



- Endemic in Southeast Asia (particularly Thailand) and Northern Australia
- Global spreading, severely underreported
- Global minimal burden 165'000 cases/year, with a mortality rate of 54%

D Limmathurotsakul et al. Nature Microbiology Letters 2016

Current Treatment and its Limitations

- Melioidosis is very difficult to treat due to intrinsic resistance of B. *pseudomallei* to many established classes of antibiotics

- Current melioidosis therapy is biphasic
  - High-dose short term parenteral acute phase
  - Long term oral eradication phase

- Acute phase treatment for 10-14 days by intravenous ceftazidime
  - Or a carbapenem
- Followed by 12-20 weeks oral eradication by trimethoprim-sulfamethoxazole with or without doxycycline
  - High relapse rates

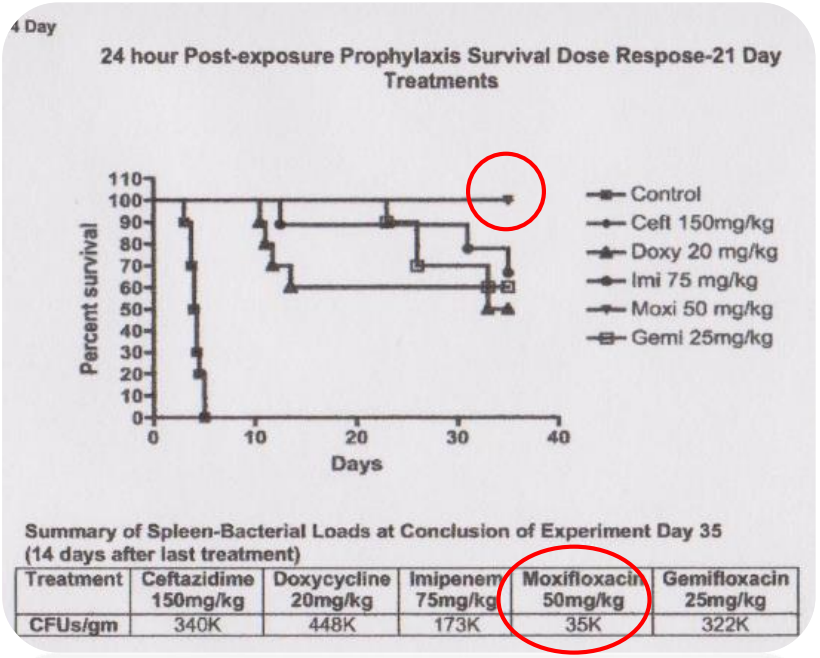
- **In a nutshell:**
  - **No early diagnosis tools and no affordable, oral treatment for the acute phase are currently available**

Approach 1: Repurposing Existing Drugs

- Bp shows intrinsic resistance against many established classes of antibiotics, but not all and not all «generations»
- The antibiotics have to work intracellularly
- Only a limited number of antibiotics have been tested against Bp or B. thailandensis

- It is therefore proposed to identify candidate antibiotics with superior intracellular activity from screening the full battery of available antibiotics in an intracellular invasion assay
- Efficacy to be confirmed in either a rodent or NHP model of Bp infection

- Moxifloxacin...



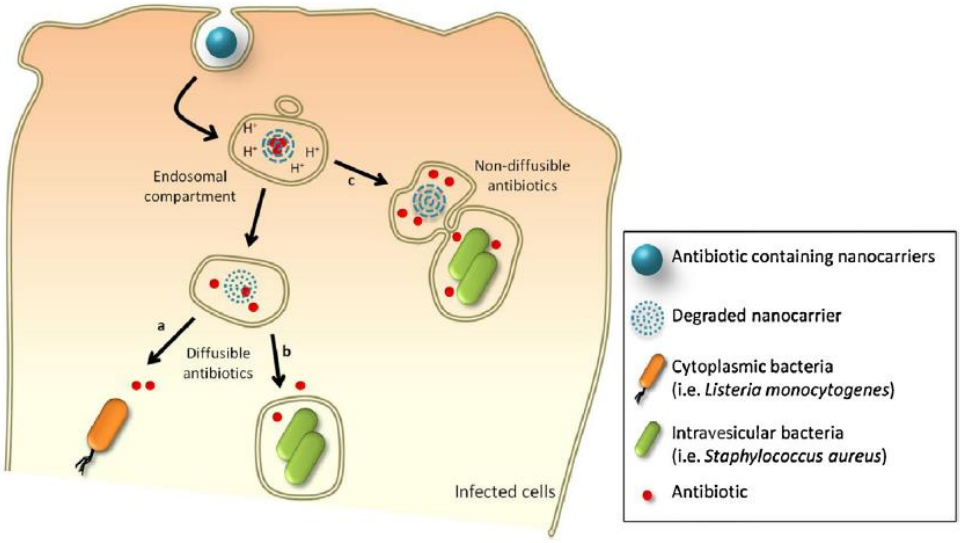
Treatment	Ceftazidime 150mg/kg	Doxycycline 20mg/kg	Imipenem 75mg/kg	Moxifloxacin 50mg/kg	Gemifloxacin 25mg/kg
CFUs/gm	340K	448K	173K	35K	322K

Murine aerosol-challenge model

HS Heine et al. US AMRI ICAAC poster E-1634 2010

Approach 2: Nanocarriers

- Many highly potent antibiotics do not reach intracellular bacteria
  - Permeability barrier
  - Intracellular sublocation
  - Low intracellular retention
- Nanocarriers are able to improve intracellular residence time
  - Polymeric nanoparticles
  - Liposomes
  - Dendrimers
  - Polymersomes et al
- Leads from approach 1 tested with different nanocarriers

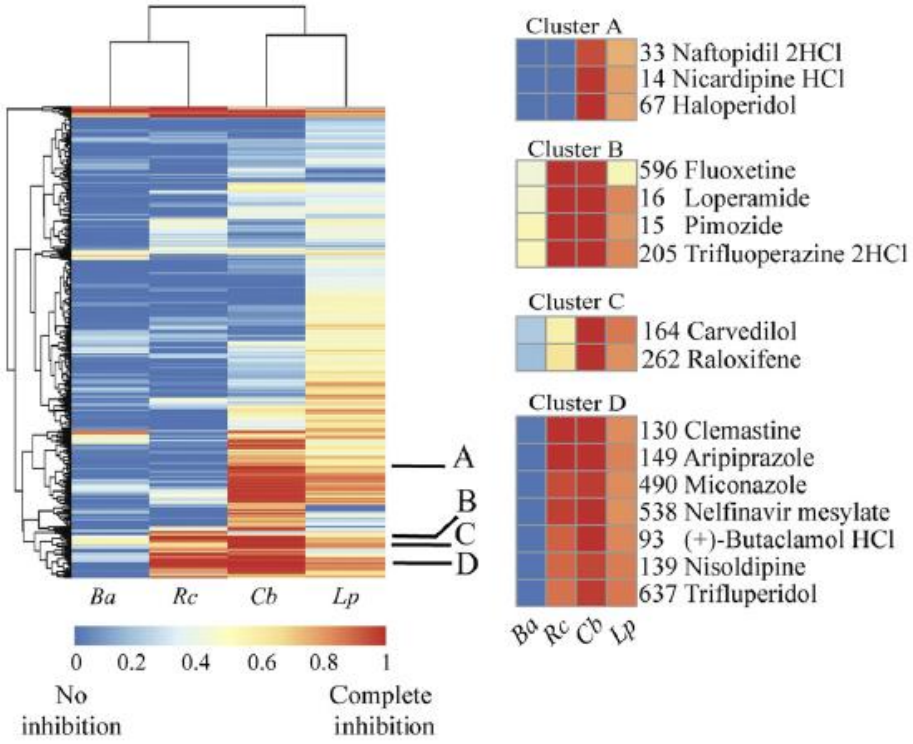


Intracellular delivery of antibiotics

Abed N and Couvreur P. International Journal of Antimicrobial Agents 2014

Approach 3: Combination with HDA-Drugs

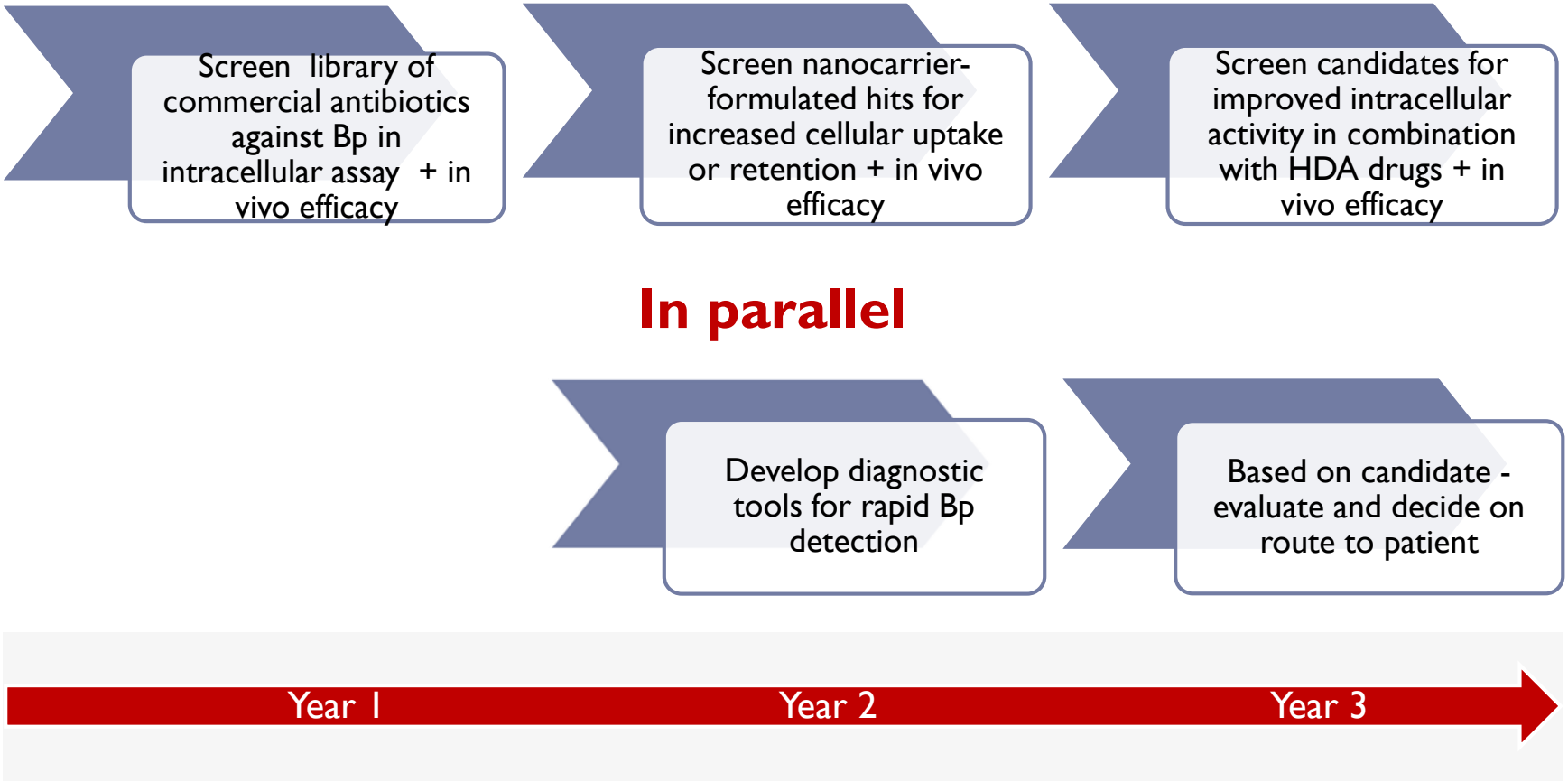
- A collection of FDA approved drugs revealed numerous drugs with indirect inhibition of intracellular bacteria
- They cluster in
  - GPCR antagonists
  - Calcium trafficking
  - Sterol homeostasis
- Some act post-infection
- Ideally to be combined with direct antimicrobial agent (leads from approaches 1 and 2)



Ba = Brucella abortis
Rc = Rickettsia conorii
Cb = Coxiella burnetii
Lp = Legionella pneumophila

Czyz DM et al. mBio 2014

Flowchart and Budget for Clinical Candidate



Budget greatly depending on type of animal model:
Somewhere between 1.5 to 3 mill US$ in total

Handing over to Joseph Larsen (BARDA) for Diagnostics, NHP models and «Animal Rule»

Thank you for your interest!