Preclinical update - highlights of the recently published studies about respiratory chain inhibitors efficacy against leprosy

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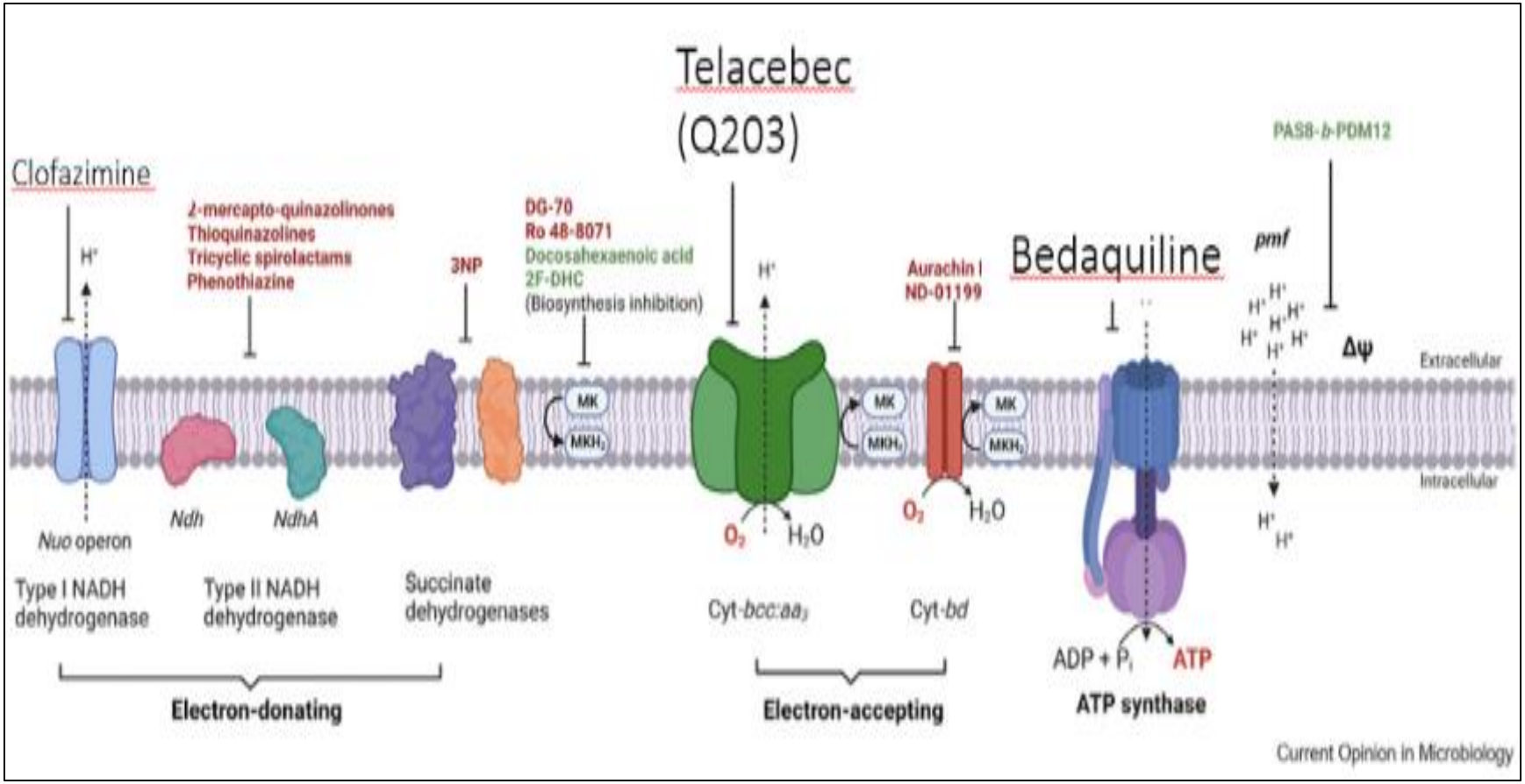
ILC – Bali - 07/07/2025

Respiratory vulnerability in mycobacteria



First regulatory approval of a new antiTB drug after 40 years of inattention

Clinical Trial > Science. 2005 Jan 14;307(5707):223-7. doi: 10.1126/science.1106753. Epub 2004 Dec 9.

A diarylquinoline drug active on the ATP synthase of Mycobacterium tuberculosis

Koen Andries [1], Peter Verhasselt, Jerome Guillemont, Hinrich W H Göhlmann, Jean-Marc Neefs, Hans Winkler, Jef Van Gestel, Philip Timmerman, Min Zhu, Ennis Lee, Peter Williams, Didier de Chaffoy, Emma Huitric, Sven Hoffner, Emmanuelle Cambau, Chantal Truffot-Pernot, Nacer Lounis, Vincent Jarlier

Reference mouse foot-pad model

⇒ the **proportional bactericidal mouse foot-pad model technique remains the only technique capable of discriminating between viable**, *i.e.* capable of multiplication, and **non-viable,** *i.e.* incapable of multiplication, *M. leprae,* and also **quantifying the rate of bacterial killing by drugs**

→ **threshold** for measuring the percentage of viable bacilli **= 0.00006-0.004**

Bedaquiline for leprosy (1)

TABLE 2. Bactericidal activities against *M. leprae* 17543 (second experiment) or Thai 53 (third experiment) of several antimicrobial agents, measured with mice by the proportional bactericidal method

Expt	Treatment[a]	% Viable *M. leprae*	% Viable *M. leprae* killed by treatment
Third	None (control)	0.123	
	R207910, 25 mg/kg	0.006[b]	95.1
	MIN, 25 mg/kg	0.028[c]	77.2
	MXF, 150 mg/kg	0.011[b]	91.1
	RIF, 10 mg/kg	0.014[b]	88.6
	RFP, 10 mg/kg	<0.006[b]	>95.1
	MXF-MIN	<0.006[b]	>95.1
	MXF-R207910	<0.006[b]	>95.1
	RFP-MXF-MIN (PMM)	<0.006[b]	>95.1
	RFP-MXF-R207910	<0.006[b]	>95.1

[a] All drugs were administered by gavage as a single dose. Abbreviations: MIN, minocycline; MXF, moxifloxacin; RFP, rifapentine; RIF, rifampin.
[b] Significantly lower than that for untreated control group in the same experiment.
[c] Not significantly different from that for untreated control group in the same experiment.

(Ji, AAC 2006)

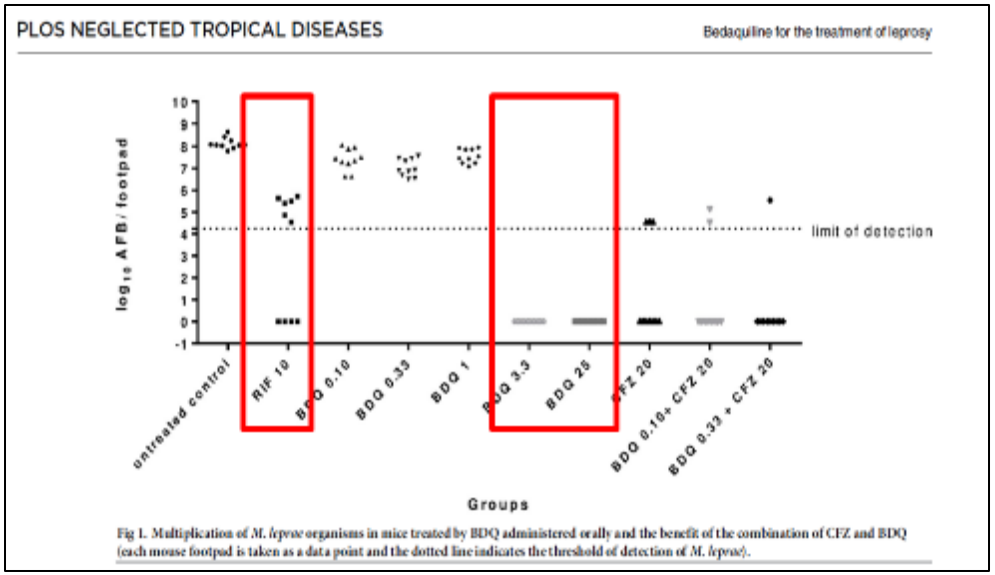


Fig 1. Multiplication of *M. leprae* organisms in mice treated by BDQ administered orally and the benefit of the combination of CFZ and BDQ (each mouse footpad is taken as a data point and the dotted line indicates the threshold of detection of *M. leprae*).

(Chauffour, PNTD, 2023)

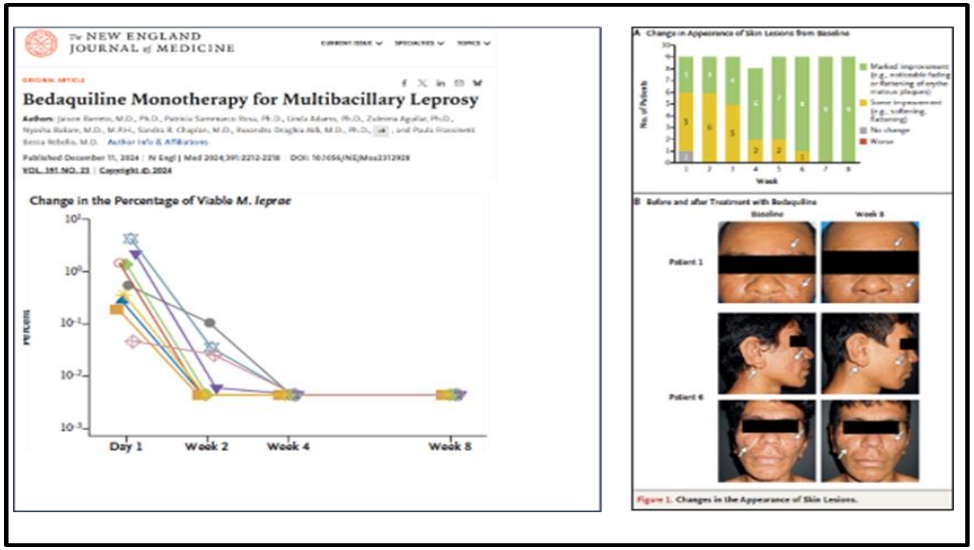
→ bactericidal effect

→ single dose of bedaquiline > rifampicin and moxifloxacin

- the main mechansim of resistance to bedaquiline in tuberculosis = mutation in Rv0678, encoding a repressor of a efflux pump
- the rv0678-mmpS5 mmpL5 locus is absent in *Mycobacterium leprae* (*M. ulcerans)* (Hartkoon et al. 2014)

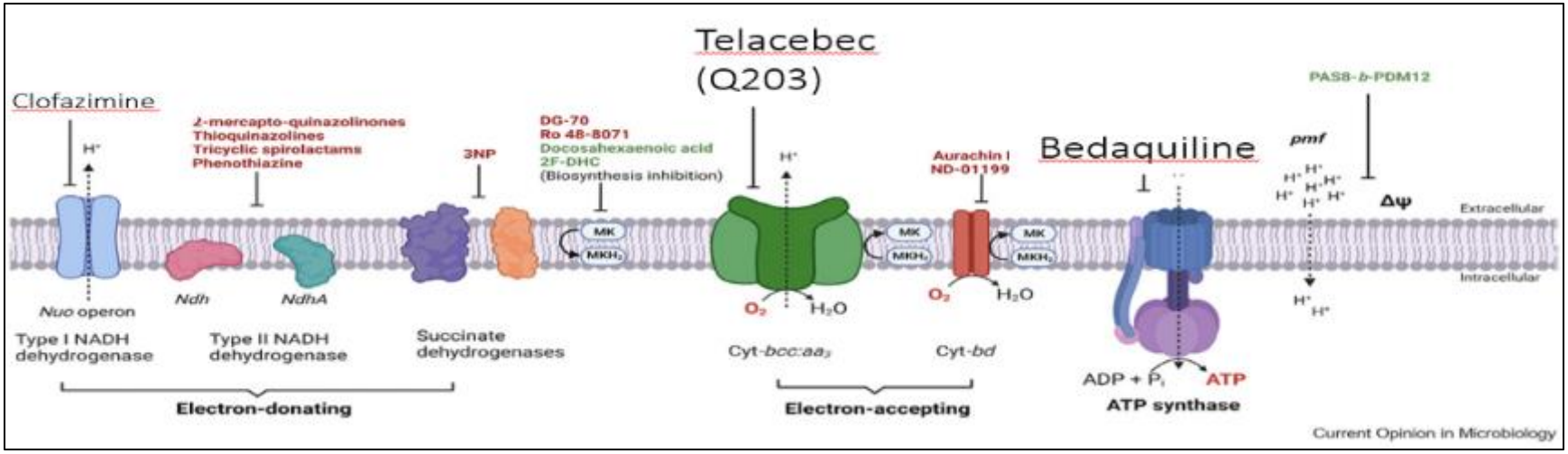
Bedaquiline for leprosy (2)

- Two recent clinical trials
- 8 weeks BDQ (200 mg/d – 2 weeks / 100 mg 3 t/week – 6 weeks)
  Followed by MDT for 1 year
- **Common endpoint** = rate of bacterial killing measured by the reference **proportional bactericidal mouse foot-pad model technique**
- Exploratory endpoints = molecular biomarkers (cf. Charlotte Avanzi's talk)



⇒ in patients with multibacillary leprosy, bedaquiline monotherapy cleared *M. leprae* by 4 weeks of treatment and led to improvement in the appearance of skin lesions by 7 weeks

Telacebec for leprosy (1)



Mechanism of resistance / escape to telacebec in *M. tuberculosis*:

- **"escape" possible due to the presence of another electron acceptor** (cytochrome bd (cyt-bd) in *M. tuberculosis* (Kalia NP, Sci Rep. 2019, doi: 10.1038/s41598-019-44887-9)
- **mechanism of resistance: mutations in the target** (especially QcrB encoding one of the cytochrome bc subunits) (Scherr, Nat Commun. 2018, doi: 10.1038/s41467-018-07804-8; Pethe K, Nat Med. 2013, doi: 10.1038/nm.3262)

⇒ absence of cytochrome bd in the *M. leprae* respiratory chain, as in *M. ulcerans*
⇒ no "escape mechanisms " possible

Telacebec for leprosy (2)

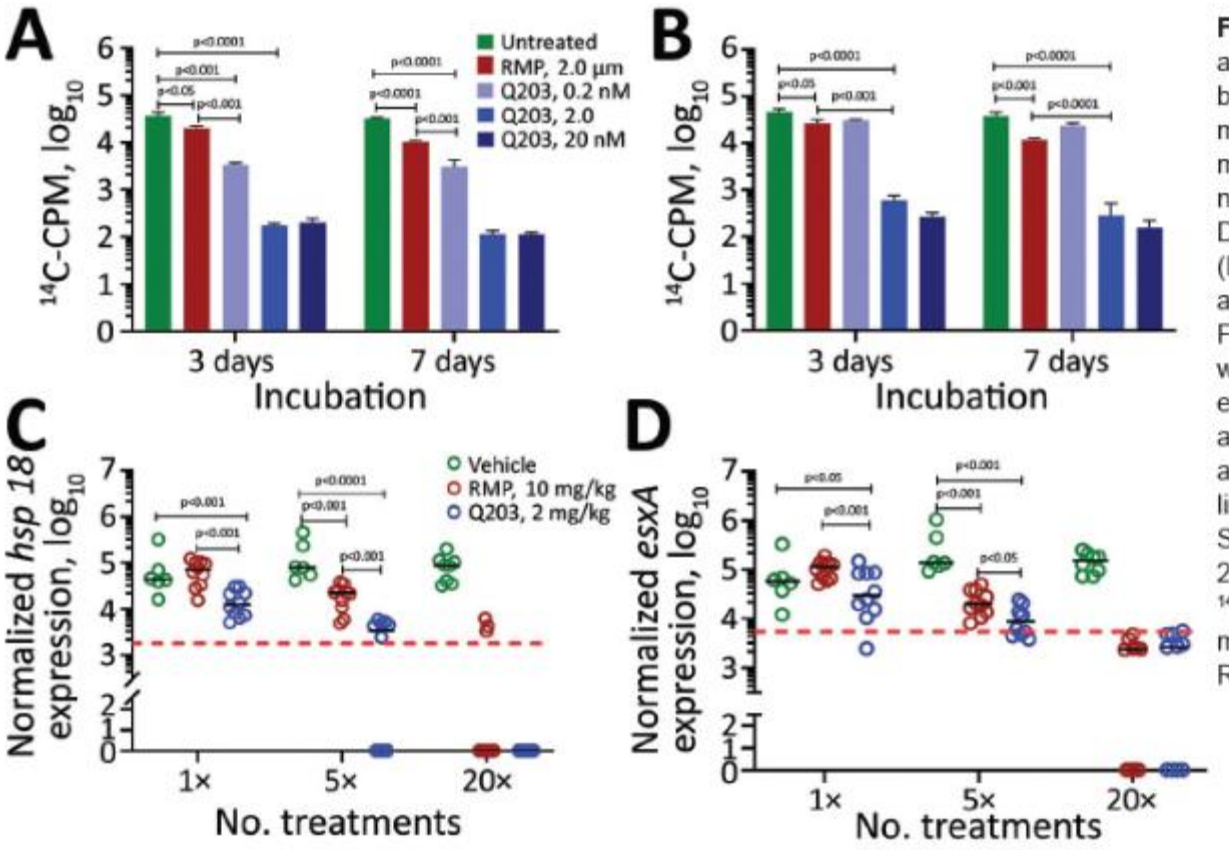


Figure. Efficacy of telacebec against *Mycobacterium leprae* bacteria in axenic culture (A), in murine bone marrow–derived macrophages (B), and in athymic nude mouse foot pad model (C, D). *M. leprae hsp18* (C) and *esxA* (D) expression levels were used as a surrogate measure of viability. For panels A and B, the assays were performed in triplicate for each condition. For panels C and D, each foot pad is taken as a data point, and the red dotted lines indicate ≈99% *M. leprae* kill. Significance was determined by 2-tailed unpaired Student *t*-test. ^{14}C, carbon 14; CPM, counts per minute; Q203, telacebec; RMP, rifampin.

(Lahiri, EID, 2022)

→ although >5 consecutive doses of rifampin were needed to detect a bactericidal efficacy, 1 dose of telacebec at a low dose of 2 mg/kg was sufficient to reduce the bacterial viability substantially

Dr. Ramanuj Lahiri
NHDP, LA, USA

PLOS Neglected Tropical Diseases

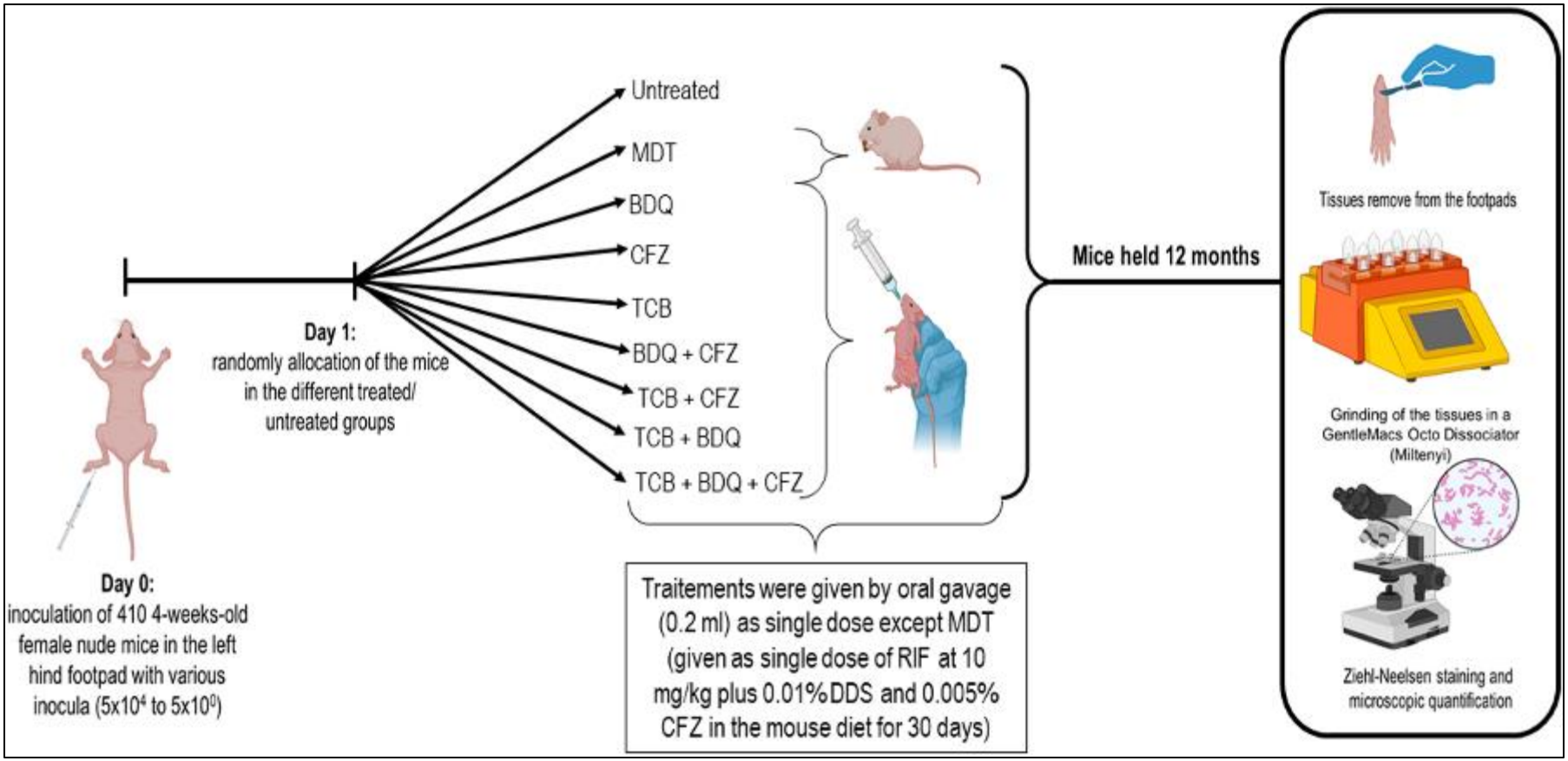
RESEARCH ARTICLE

Unprecedented *in vivo* activity of telacebec against *Mycobacterium leprae*

Aurélie Chauffour[1], Emmanuelle Cambau[2], Kevin Pethe[3,4,5], Nicolas Veziris[1,6], Alexandra Aubry[1,4,6]

Fondation Raoul Follereau
Fondation reconnue d'utilité publique

2025



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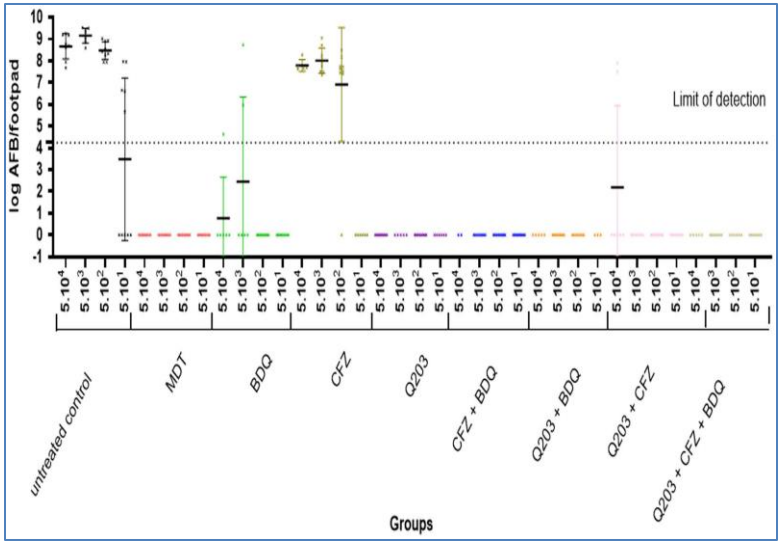
Treatment	% viable *M. leprae*	% viable *M. leprae* killed by treatment[d]	P value for comparison with: untreated control[e]	MDT[f]
Untreated control	1.840	-	-	-
MDT[a]	<0.0004	≥99.9	<0.001	-
BDQ 25 mg/kg	0.001	99.6	<0.001	0.06
CFZ 20 mg/kg	0.436	76.3	0.0026	0.003
TCB 10 mg/kg	<0.0004	≥99.9	<0.001	ns
CFZ + BDQ	<0.0004	≥99.9	<0.001	ns
TCB + BDQ	<0.0004	≥99.9	<0.001	ns
* TCB + CFZ	0.001	99.9	<0.001	0.121
* TCB + CFZ + BDQ	<0.0004	≥99.9	<0.001	ns



→ telacebec is the sole achieving the absence of AFB in all mouse footpads, as the standard

→ when comparing bitherapy groups, all, except the combination of telacebec and CFZ, achieved the absence of AFB in all mouse footpads → antagonism?

→ not surprisingly, the combination of the three respiratory chain inhibitors achieved a similar efficacy to the standard MDT, with no mice displaying AFB

Telacebec to Control Buruli Ulcer and Leprosy in Africa (TEBULA)

Fiche descriptive

Objectif

Leprosy (Hansen disease) and Buruli ulcer are among the devastating skin neglected tropical diseases (Skin NTDs) prevalent in sub-Saharan Africa that cause progressive and permanent disabilities, exposing the patients and their families to discrimination, social stigma, and economic burden, adding complex challenges to communities already exposed to extreme inequality. Considering the needs of the most affected populations, children and people living in rural remote areas, current treatments are suboptimal in their complexity and length. Treating leprosy requires multiple drugs administered for 6 to 12 months. Buruli ulcer treatment requires 3 pills daily at different hours for two months, and lesion healing can take up to 12 months. Both treatments are associated with significant side effects (skin discoloration from clofazimine, exacerbating the stigma that leprosy patients face, and potentially fatal hypersensitivity to dapsone).

This proposal aims to transform the treatment of Buruli ulcer and leprosy using the novel compound telacebec. Telacebec has demonstrated profound activity against Mycobacterium ulcerans and Mycobacterium leprae, the causative agents of Buruli ulcer and leprosy, respectively, whose evolutionary biology has rendered them hypersusceptible to killing by telacebec. We propose to conduct two clinical trials with telacebec-based treatment regimens that will cure Buruli ulcer and leprosy with fewer drugs, shorter duration, and fewer side effects than current therapy. We will perform this work through an integrated, multidisciplinary consortium of experts with broad experience in drug development, therapeutic delivery, community engagement, stakeholder participation, policy implementation, and capacity building to achieve equitable access to a new standard of care for these diseases.

Informations projet

TEBULA
N° de convention de subvention: 101190742

DOI
10.3030/101190742

Date de signature de la CE
20 Mai 2025

Date de début
1 Juin 2025

Date de fin
31 Mai 2029

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Contribution de l'UE
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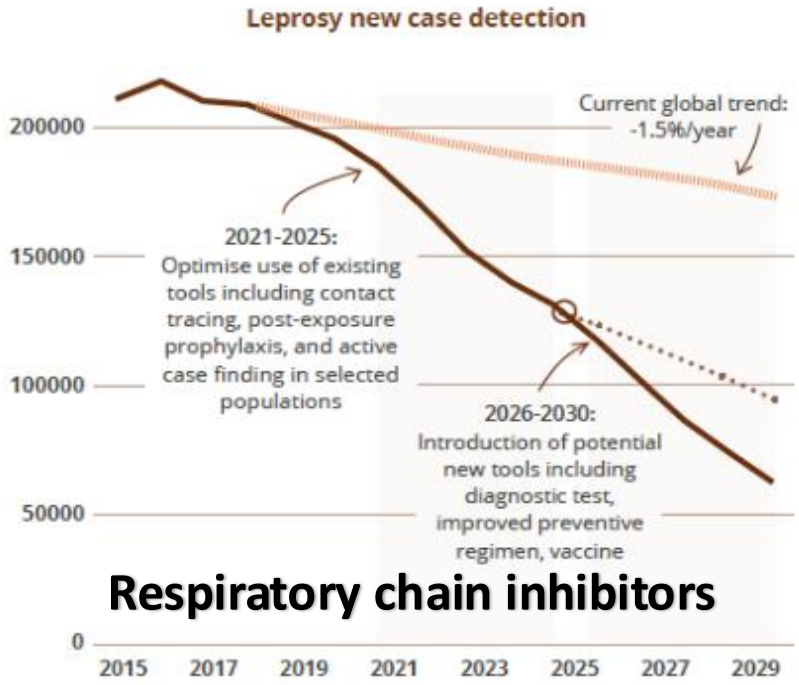
Investissement dans les priorités politiques de l'UE

Stratégie numérique ○ Air pur ○

“Zero leprosy” achievable …

WHO global leprosy strategy 2021-2030



Long term vision

Zero leprosy: zero infection and disease, zero disability, zero stigma and discrimination

Goal

Elimination of leprosy (defined as interruption of transmission/absence of disease)[21]

Global targets for 2030

- 120 countries reporting zero new autochthonous cases
- 70% reduction* in annual number of new cases detected
- 90% reduction* in rate per million population of new cases with G2D
- 90% reduction* in rate per million children of new child cases with leprosy

** from 2020 projected baseline*

These are global targets. Countries will set targets relevant to their own leprosy situation and baseline data in order to contribute to the achievement of global targets. Strategic evaluations will be undertaken by WHO after 2023 and 2025 to assess progress and consider the need for course corrections or amended targets.

⇒ respiratory chain inhibitors might be game changer for leprosy as they can allow simpler, shorter, more effective and safe treatment/prophylaxis