The Coming Revolution: New Paradigms in the Development of Drugs for HIV/AIDS, Tuberculosis, Malaria, and Emerging Infectious Diseases

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Economics of drug development - 2008*

- Only 1 in 30,000 screened chemicals becomes a licensed drug.
- Only 1 in 10 drugs that enter clinical testing becomes a licensed drug.
- Only 1 in 5 licensed drugs ever generates enough revenue to cover research and development (R&D) expenditures.

*Source: U.S. Pharmaceutical Research and Manufacturers Assoc.

Economics of drug development - 2008

- It costs on average $0.8-1.0 billion to get a new drug developed and licensed.
- Average length of time from patent filing to NDA approval is 8-10 years.
- Expected annual revenues must be $50 – 100 million.
- Focus on “blockbuster” drugs.

Economics of drug development - 2008

- Competition between generic and "branded" prescription drugs:
  - 2003: Generics are 54% of treatments dispensed in the U.S.
  - 2008: Generics are 69% of treatments dispensed in the U.S.

Emerging infections - 2008

- Continued spread of communicable diseases with limited treatment options:
  - MDR- and XDR-tuberculosis
  - Drug-resistant malaria
  - H5N1 and avian influenza strains
  - Drug-resistant HIV
- Continued risk of intermittent outbreaks of communicable diseases with limited treatment options:
  - SARS
  - Dengue fever
  - Ebola

Drug Development and Emerging Infections - 2008

The Problem:

- Most of the disease burden of emerging and global infectious diseases is occurring in resource-poor countries unable to afford expensive therapies.
- Current business models for new drug development cannot be easily applied to the most important emerging infectious diseases.

Drug Development and Emerging Infections - 2008

Important Problems:

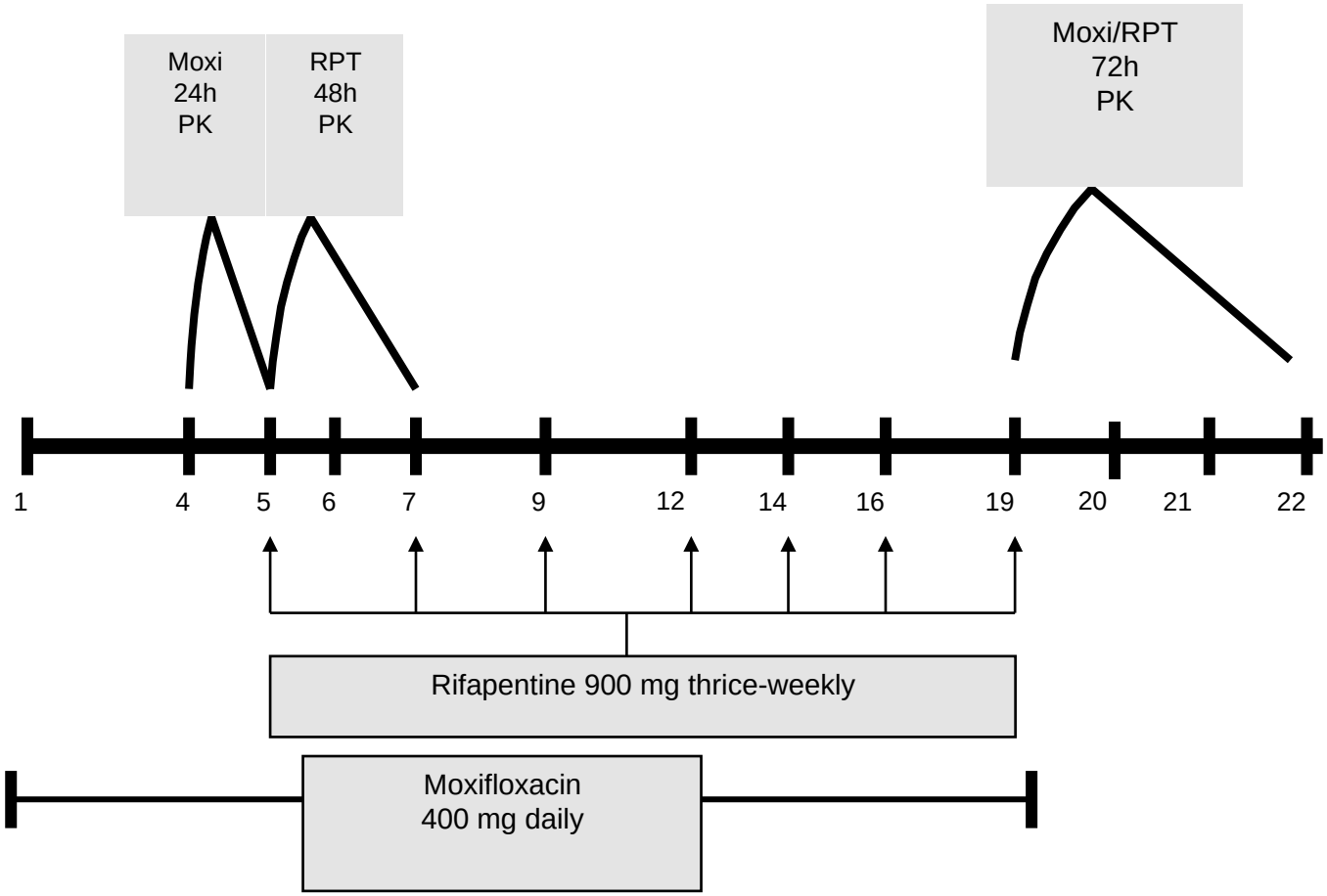
Metabolic drug interactions affecting new agents targeting MDR- and XDR-TB.

Rifapentine plus Moxifloxacin

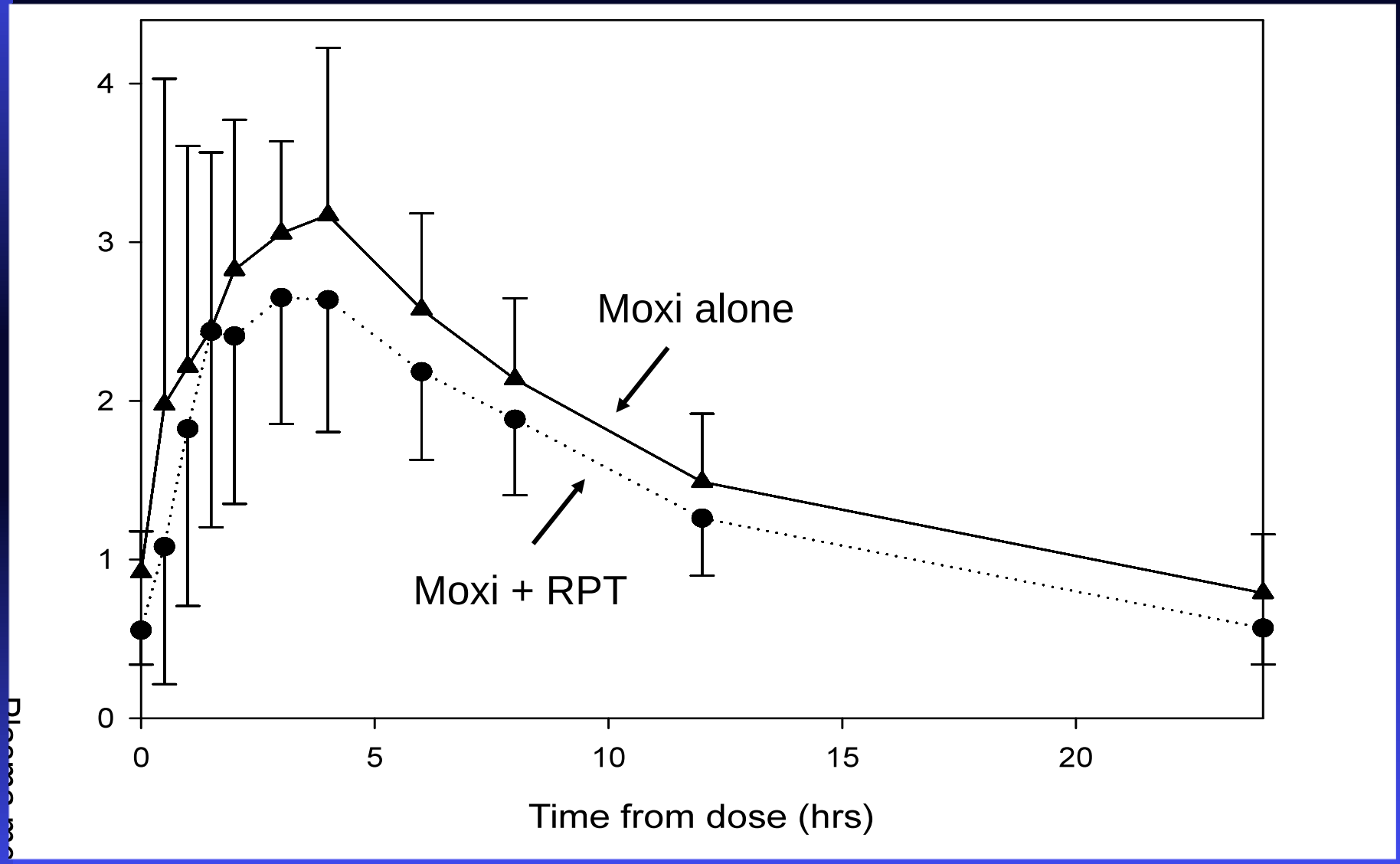
The problem:

- Rifapentine could induce moxifloxacin metabolism, decrease moxi concentrations, and reduce moxi's anti-TB activity.

Study Design: PK interactions between rifapentine and moxifloxacin



Effect of RPT on Moxi Concentrations



Dooley et al, *Antimicrob Agents Chemother* 2008;52:4037-42

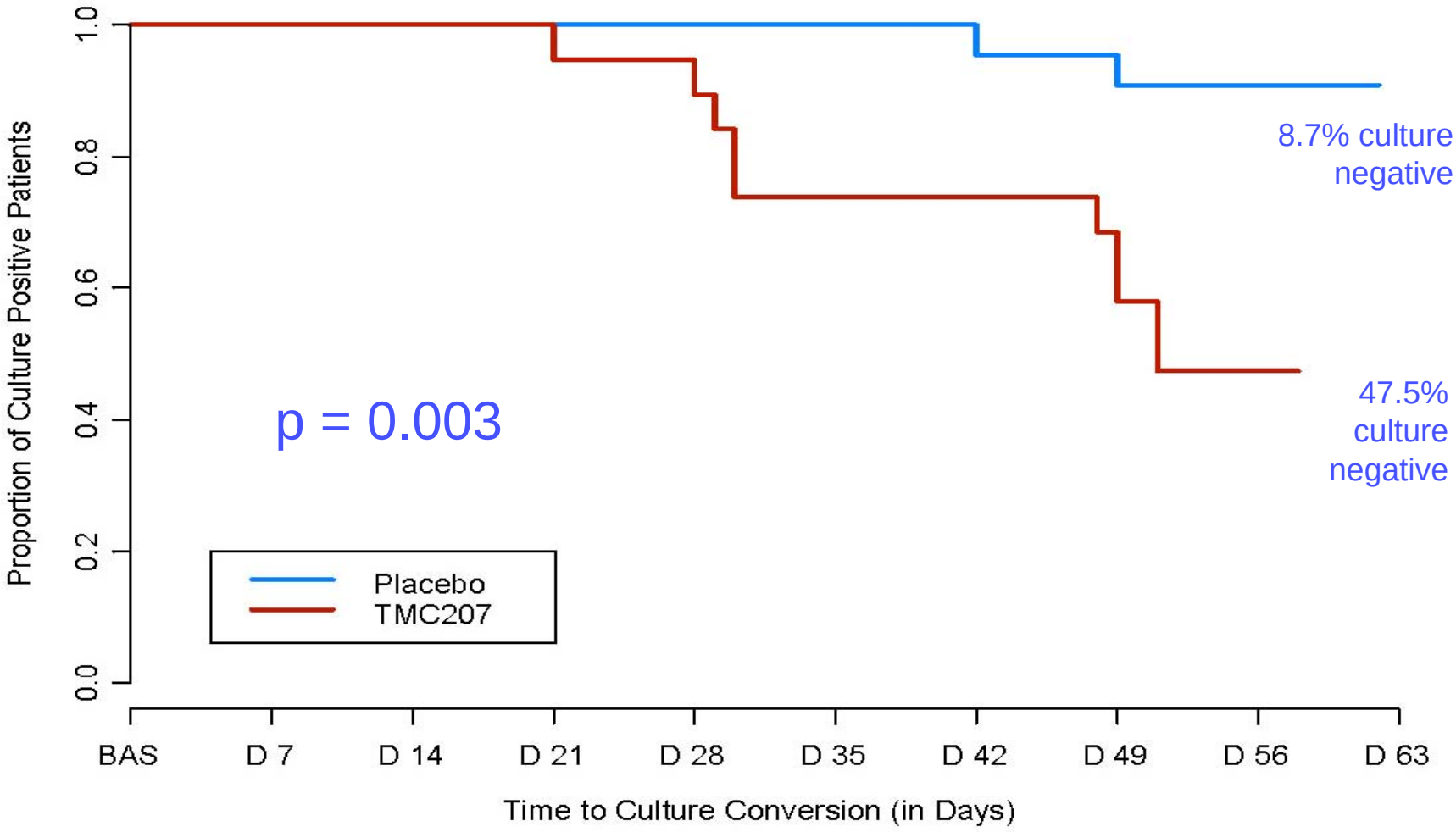
TMC-207:

The poster child for not-for-profit drug development?

TMC-207

- A diarylquinoline with activity against drug-sensitive and drug-resistant TB, including XDR-TB.
- Inhibits the proton pump function of mycobacterial ATP synthase -- a novel mechanism of action.
- Intracellular [ATP] is significantly lower in hypoxic nonreplicating *M. tuberculosis*, which are more susceptible to ATP depletion.
- TMC-207 may be uniquely bactericidal and sterilizing for nonreplicating MTB, allowing dramatic shortening of the course of treatment.

TMC207: culture conversion at 8 weeks



Diacon et al., *ICAAC* 2008; LB abstract

Drug Development and Emerging Infections - 2008

The Problem:

- New drugs for the most serious endemic and emerging infectious diseases will face the same problems in clinical development faced by any drug.
- Not possible to take shortcuts in clinical research, even for drugs targeted to the developing world.

Solutions???

Possible Solutions

- New sources of funding to develop drugs for emerging infections and diseases of RPC's?
  - Foundations
  - NGO's
  - Governments
- Low profit margin companies?
  - Generic manufacturers
- Not-for-profit companies?
- Less expensive pathways to develop and approve drugs?

Possible solutions:
Low profit margin companies?

THE ECONOMIC TIMES

Ranbaxy set to launch India's first malaria drug

5 Jul, 2008, 0145 hrs IST, ET Bureau

NEW DELHI: India may have its own anti-malaria drug soon. Drug major Ranbaxy has successfully completed the phase II clinical trials for the first malaria drug being developed in the country. The company is expected to start marketing the drug three to five years from now.

"The proof-of-phasing for phase II of the trials have been successfully undertaken and the drug will now undergo phase III of trials before being introduced in the market," Ranbaxy's senior VP for new drug discovery research Pradip Bhatnagar said on the sidelines of a seminar. Ranbaxy has been working on the anti-malaria segment since May 2003. Earlier, it was a collaborative research project with the Geneva-based Medicines for Malaria Venture (MMV) to develop the synthetic peroxide anti-malarial drug but MMV walked out of the joint project in November 2007.

The company has not yet decided on any trade name for the drug research. The company plans to export the anti-malaria drug to Asian, African and South American countries at an affordable cost. Despite having a large market for malaria in developing countries, the market segment has very limited resources.

Possible problems:
Low profit margin companies

A List of Drugs Manufactured at the Dewas and Paonta Sahib Facilities of Ranbaxy Laboratories, Ltd.

Department of Health and Human Services

Finished Drugs

- Acyclovir
- Amoxicillin
- Amoxicillin and Clavulanate Potassium
- Carbidopa and Levodopa
- Cefaclor
- Cefadroxil
- Cefpodoxime Proxetil
- Cefprozil
- Cefuroxime Axetil
- Cephalexin
- Ciprofloxacin HCl
- Clarithromycin
- Fenofibrate
- Fluconazole
- Fosinopril Sodium
- Fosinopril Sodium and Hydrochlorothiazide
- Gabapentin
- Ganciclovir Sodium *
- Glimepiride
- Isotretinoin
- Lamivudine
- Loratadine (OTC)
- Metformin HCl
- Nefazodone HCl
- Nitrofurantoin; Nitrofurantoin and Macrocrystalline
- Ofloxacin
- Pravastatin Sodium
- Ranitidine
- Simvastatin *
- Terazosin HCl
- Valacyclovir HCl
- Zidovudine (PEPFAR)

* Products not affected by Import Alert.

-FDA Website 09/17/2008

Possible solutions:
Not-for-profit companies?

Table 1 Survey of portfolio-based nonprofit biomedical firms, 2008

Name	Primary purpose	Primary population focus	Primary disease focus	Products in clinical trials/ approved	Year of formation	Annual budget	Major grants
Institute for Applied Biomedicine (http://www.appliedbiomed.org)	Financing, development, preclinical testing	Global health	Immune system–based treatments for HIV, autoimmune disorders	Immudel-gp120	1996	$31,236	
Global Solutions for Infectious Diseases (http://www.gsid.org)	Financing, development, and testing	Global health	HIV vaccine, pediatric dengue vaccine		2004	$1,019,073	Gates Foundation, $7.9 million (2006, HIV)
Institute for OneWorld Health (http://www.iowh.org)	Financing, development, and testing	Global health	Anti-infectives	Artemisinic acid/ paromomycin i.m. injection	1998	$23,391,795	Gates Foundation, $42.5 million (2004, artemisin); Gates Foundation, $10 million (2005, paromomycin); Gates Foundation, $46 million (2006, antidiarrhea program)
International Partnership for Microbicides (http://www.ipm-microbicides.org)	Financing, coordination, development, delivery	Women, global health	HIV transmission prevention	Dapivirine, L'644	2002	$18,775,834	
Alfred Mann Foundation (http://www.aemf.org)	Financing, development, and testing	Developed world	Physical medical impairments	Glucose sensor, cochlear implant, implantable microstimulator	1985	$20,735,358	
Institute for Pediatric Innovation (http://www.pediatricinnovation.org)	Financing, development, and testing	Children, developed world	Pediatric NICU, pediatric cardiology		2006	$43,260	

- Conti et al. *Clin Pharmacol Ther* 2008; 84:194

Institute for OneWorld Health
A Nonprofit Pharmaceutical Company

About Us | Business Model | Global Health | Diseases & Programs | How to Get Involved | Media Center

Dr. Victoria Hale Inducted into the Institute of Medicine of the National Academies in October 2008!

Those elected to the Institute of Medicine's membership have made major contributions to the advancement of the medical sciences, health care, and public health.

Learn more

INTERNATIONAL PARTNERSHIP for MICROBICIDES

Developing HIV-Prevention Options for Women Worldwide

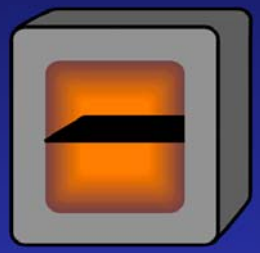
MERCK

Possible solutions:
Less expensive pathways
to develop and approve drugs?

Accelerator Mass Spectrometry: The Approach

- Existing methods to measure intracellular NRTI phosphates are expensive, time consuming, and require large blood volumes.
- AMS is an extremely sensitive technique that can be used to measure ^{14}C-labeled compounds in human cells, tissues, and body fluids.
  - Limits of detection in the attogram to zeptogram range (10^{-18} to 10^{-21} grams)
- Drawbacks include:
  - Inability to distinguish metabolites from parent drug
  - Very long half-life of ^{14}C
  - Small number of facilities with this technology

1.Cryogenic transfer



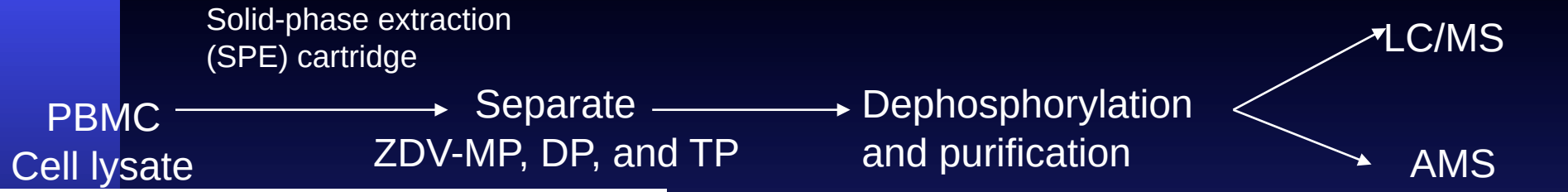
2.Reduction to graphite

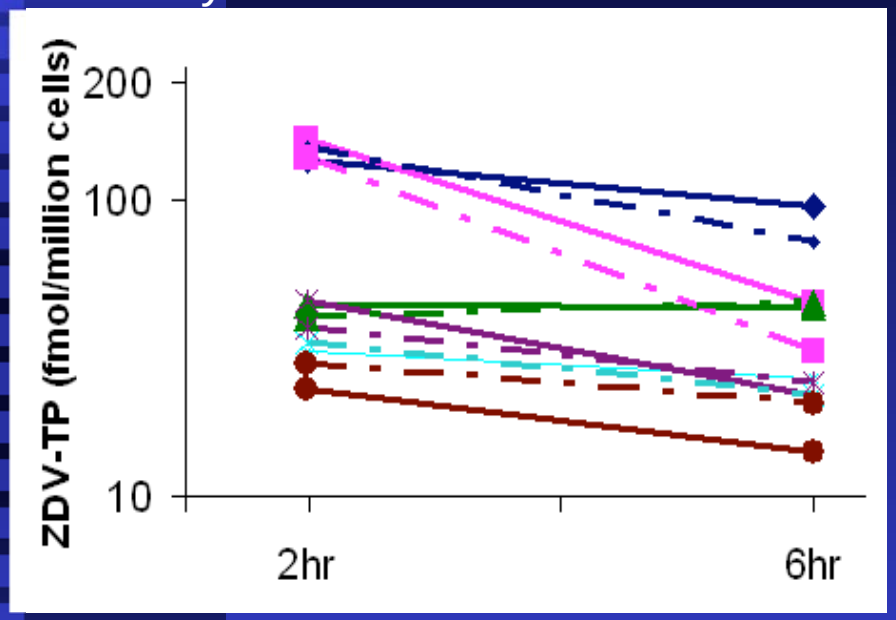
3. Count isotopic ratio of $^{14}C/^{12}C$ atomic nuclei

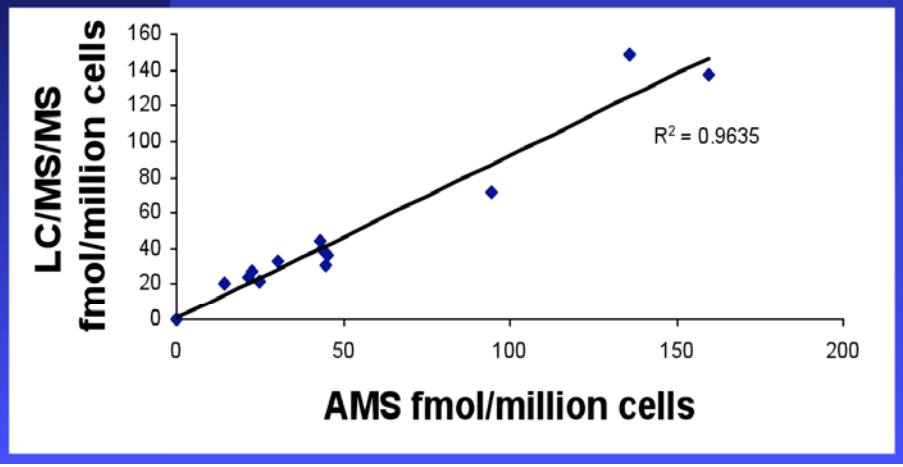
Accelerator Mass Spectrometry: Potential applications in clinical pharmacology and drug development

- Microdosing studies
  - Clinical drug development at an early stage (Phase zero)
- Drug Metabolism and Distribution
  - Better sensitivity than LC/MS
  - Able to detect unknown/multiple metabolites
- FDA allows up to 100 ug of an investigational drug in Phase 0, or up to 1 milliCurie exposure (though 100-200 nCi adequate for detection in plasma)
- Identify the most promising clinical leads for $50,000 - $100,000 per compound

Accelerator Mass Spectrometry: Proof-of-concept







- ZDV-TP concentrations were consistent with previous reports.
- The mean 2h and 6h ZDV-TP concentrations were similar comparing AMS and LC/MS/MS
- Estimated half-life of 4h was consistent with previous reports.
- AMS was about 30,000-fold more sensitive than LC/MS/MS for measuring ZDV-TP

J. Chen et al., 16th CROI 2009, abstract 704

The Ivermectin Paradigm:

Synergy between for-profit and not-for-profit applications

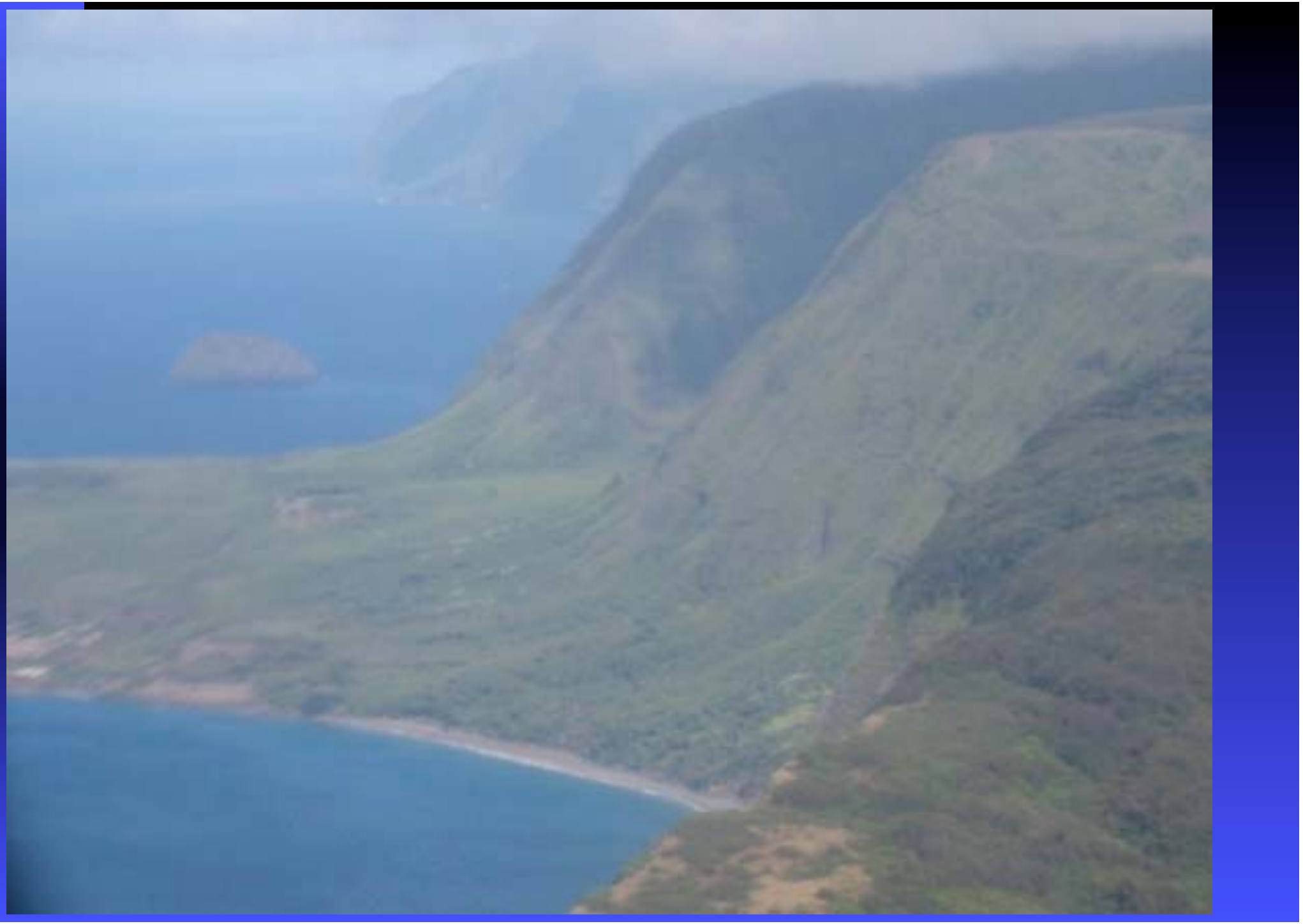
The Ivermectin Paradigm:

Can it happen again?


ALOHA
SLOW DOWN
THIS IS
MOLOKA`I
MAHALO


MOLOKA'I
Aloha


MOLOKA'I
Aloha

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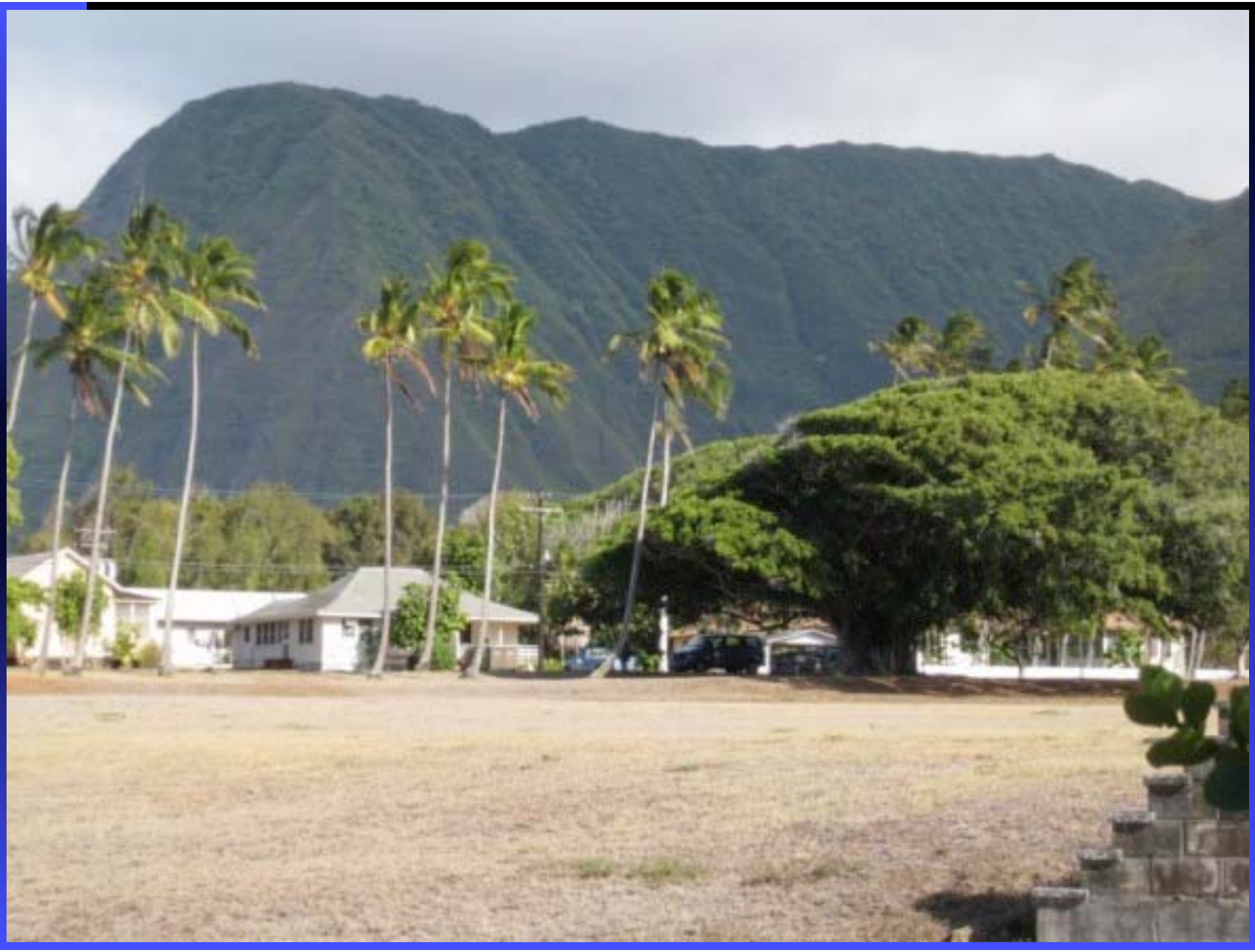


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CHECK OUT TIME 12:00 NOON
ALL PERSONAL BELONGINGS
MUST BE OUT BY
CHECK OUT TIME


FATHER


PATIENTS

Principles of Antimycobacterial Chemotherapy

Current Treatment Guidelines for Leprosy

- Pauci-bacillary (PB) leprosy (1-5 skin lesions): Regimen of two drugs – Rifampin and Dapsone for 6 months
- Multi-bacillary (MB) leprosy (>5 skin lesions): Regimen of three drugs – Rifampin, Clofazimine and Dapsone for 12 months

Will next eradicated disease be leprosy?

by Marie Rosenthal
Managing Editor

GENEVA, Switzerland—The World Health Organization (WHO) believes leprosy, like smallpox, could be eliminated worldwide.

"Eliminating leprosy as a public health problem before the year 2000 is no longer a dream," said Shaik K. Noordeen, MD, chief of WHO's Leprosy Unit. "We have the know-how, the determination and the necessary network to achieve this."

Lo faremo

Lo faremo
Non perche si puo,

Lo faremo
non perche si puo,
ma perche si deve.

Acknowledgements (1)

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