EDCTP Stakeholder Meeting
Tuberculosis
Paris - October 28, 2013

TUBERCULOSIS: REMAINING CHALLENGES

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Director: ANRS & IMMI/AVIESAN
The French Alliance for Life and Health Sciences: Aviesan

- Created in April 2009
- To coordinate the strategic analysis, the scientific programming and the operational implementation of research

  - **Research operating agencies:**
    - Inserm (ANRS & INCA)
    - CNRS life sciences department
    - CEA (atomic energy commission)
    - Inra (national institute for agricultural research)
    - Inria (computer science and automatic control)
    - IRD (research for development)
    - Pasteur Institute
    - **CIRAD, Fondation Mérieux, IRBA**

- **Universities**
- **Hospitals**
Aviesan - Alliance nationale pour les Sciences de la Vie et de la Santé
Ten Thematic Institutes

Genetics, Genomics, Bioinformatics

Cell Biology Development

Neurosciences
Cognitive Sciences
Neurology, Psychiatry
Alzheimer

Immunology
Hematology
Respiratory diseases

Microbiology
Infectious Diseases
ANRS

Molecular and Structural Biology

Nutrition Circulation Metabolism

Cancer
INCa

Public Health
IReSP

Health Technologies
Main Research Institutes in the field

National Institute for Health and Medical Research
Total budget: €750m

Institut Pasteur
Total Budget: €250m

National Center for Scientific Research
Total budget: €3,415bn for 7 institutes

Institute for Research for Development
Total budget: €233m

Agricultural Research Center for Development
Total budget: €214m
Project Funding/year: infectious diseases

PHRC: Clinical Research Hospital Programme
€16m/year

National Research Agency
€22m/year

National Research Agency for AIDS & Hepatitis
€39m/year

EP7, EDCTP1, IMI, JPI
ERANET €40m/year
IBEID

€1.5bn

alliance nationale
pour les sciences de la vie et de la santé

French Clinical Research Infrastructure Network

IrD

Institut de recherche pour le développement

Instituts thématiques

Institut national de la santé et de la recherche médicale

Inserm

Cirad

Liberté • Égalité • Fraternité
République Française

Bioaster

Méditerranée Infection

Agence nationale de recherches sur le sida et les hépatites virales

ANR

Institut Pasteur

IBEID

Université Paris-Saclay

ECOFET

En ouverture jeunes d'élites dans

Université

En ouverture jeunes d'élites dans
French Network
Tuberculosis: key figures in 2013

- 8.6 million incident cases [8.3-9.0], incl. 0.45 million MDR-TB [0.30-0.60]
- 12 million prevalent cases [11-13]
- About 13% of TB cases occur among people living with HIV

**Geography:**
- Asia: 58%, Africa: 27%

**Mortality:**
- HIV-negative: 0.94 million [0.79-1.10]
- HIV-positive: 0.32 million [0.30-0.34]
Estimated incidence of TB

Zumla A. et al., NEJM 2013; 368: 745-55
TB deaths, 1990-2012

WHO global tuberculosis report 2013
Comparison of leading causes of death over the past decade, 2000 and 2011

- Ischaemic heart disease
- Stroke
- Lower respiratory infections
- COPD
- Diarrhoeal diseases
- HIV/AIDS
- Trachea bronchus, lung
- Prematurity
- Diabetes mellitus
- Road injury
- Tuberculosis

[Diagram showing the comparison of leading causes of death over the past decade, 2000 and 2011.]
TB diagnostics

Technologies in early development

- Volatile organic compounds
  - BreathLink, Menssana Research, USA
  - Prototype breath analyzer device, Next Dimensions Technology, USA

- Molecular technologies
  - Alere Q, Alere, USA
  - B-SMART, LabCorp, USA
  - Gendrive MTB/RIF ID, Epistem, UK
  - LATE-PCR, Brandeis University, USA
  - GeneXpert XDR cartridge, Cepheid, USA
  - TruArray MDR-TB, Akkoni, USA
  - INFINITIMTB Assay, AutoGenomics, USA

- Culture-based technologies
  - BNP Middlebrook, NanoLogix, USA
  - MDR-XDR TB Color Test, FIND, Switzerland/Imperial College, UK
  - TREK Sensititre MYCOTB MIC plate, Trek Diagnostic Systems/Thermo Fisher Scientific, USA

- Other technologies
  - TB Rapid Screen, Global BioDiagnostics, USA
  - TBDx, Signature Mapping Medical Sciences, USA

On the market but evidence for use not yet submitted to WHO for evaluation

- Molecular technologies
  - iCubate System, iCubate, USA
  - TB drug resistance array, Capital Bio, China
  - EasyNAT TB Diagnostic kit, Ustar Biotechnologies, China
  - Truelab/Truenat MTB, Molbio/bigtec Diagnostics, India

- Non-molecular technologies
  - Alere Determine TB-LAM, Alere, USA

Technologies endorsed by WHO

- Molecular technologies
  - Xpert MTB/RIF
  - Line probe assays (acid-fast bacilli smear-positive sputum specimens or culture-positive specimens)

- Microscopy
  - Ziehl-Neelsen and fluorescence microscopy methods

- Culture-based technologies
  - Commercial liquid culture systems and rapid speciation
  - Non-commercial culture and drug susceptibility testing methods
Percentage of new TB cases with MDR-TB

Global tuberculosis report 2012
Development pipeline for new TB drugs

Phase II: n=7

Phase III: n=4

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone

Details for projects listed can be found at www.newtbdrugs.org/pipeline and ongoing projects for which a lead compound has not been identified can be viewed at www.newtbdrugs.org/pipeline-discovery.

Combination regimens: NC-001-(J-M-Pa-Z), Phase I; NC-002-(M-Pa-Z), Phase IIb; NC-003-(C)-Pa-Z, Phase IIa; PanACEA-MAMS-TB-01-(H-R-Z-E-Q-M), Phase IIb.
Phase III trial: RIFQUIN results

- Continuation phase: combination of rifapentine and moxifloxacin once a week

- Primary endpoints: relapse during follow-up to 18 months after treatment initiation & occurrence of grade 3 or 4 adverse events

- $n=730$ with newly diagnosed smear-positive TB

- 28% HIV-positive (median CD4: 312 cells/mm$^3$)
### Phase III trial: RIFAQUIN results

<table>
<thead>
<tr>
<th></th>
<th>Month 1&amp;2</th>
<th>Month 3&amp;4</th>
<th>Month 5&amp;6</th>
<th>Dosing frequency of experimental drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CONTROL REGIMEN</strong></td>
<td>Rifampicin</td>
<td>Isoniazid</td>
<td>Ethambutol</td>
<td>Pyrazinamide</td>
</tr>
<tr>
<td><strong>STUDY REGIMEN 1</strong></td>
<td>Rifampicin</td>
<td>Moxifloxacin</td>
<td>Rifapentine</td>
<td>Ethambutol</td>
</tr>
<tr>
<td><strong>STUDY REGIMEN 2</strong></td>
<td>Rifampicin</td>
<td>Moxifloxacin</td>
<td>Rifapentine</td>
<td>Ethambutol</td>
</tr>
</tbody>
</table>

- **16 weekly doses after Month 2:** Non-inferior to control regimen
- **Inferior to control regimen**
Other phase III trials

- **OFLOTUB**: gatifloxacin instead of ethambutol, 4 months
  Efficacy and safety results will be presented by Merle C et al., The Union/CDC late-breaker session, 3 Nov. 2013, 44th Union World Conference on Lung Health, Paris

- **ReMOX**: moxifloxacin instead of ethambutol or isoniazid, 4 months
  (+ delamanid for MDR-TB)
Remaining challenges: TB & NTM

- **TB prevention**: IPT, TB vaccine

- **TB control**:
  - New molecular tools, incl. better detection of drug resist.

- **TB treatment**:
  - New regimen
  - Shortened duration
  - Less drug-drug interactions
  - MDR-TB, XDR-TB

- **NTM**: which regimen for which patient? Colonization vs. disease? Treatment outcomes? Need to reduce drug toxicity!
TB and HIV: 'cursed duet', 'deadly combination' → still a challenge in 2013

TB remains the most frequent life-threatening OI and a leading cause of death among PLWH

Diagnosis: how to use Xpert MTB/RIF? POC test???

Urine LAM: interesting alternative → more data needed

Treatment:

IRIS: definition/Δg, treatment, predictive factors (score)

IPT: 6 or 36 months? Or lifelong??? Intermittent??????