Contribution of genetic variation to pharmacokinetic variability and toxicity in patients undergoing multi-drug tuberculosis treatment in Sub-Saharan Africa: RAFAgene project

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Background

Tuberculosis (TB):
- Important cause of death in Sub-Saharan Africa
- In best-case of TB treatment scenario, \( \approx 10\% \) of patients cannot be cured
- Complex relationship between TB pathogen, drugs and host
- Genetic variability of the host might play an important role for treatment response
General Aim

- To conduct:
  - a pharmacogenetic study
  - of TB drugs (Rifampicin, Isoniazid, Ethambutol, Pyrazinamide and Gatifloxacin)
  - in TB patients in Sub-Saharan Africa
Specific aims

1. To assess the role of host genetic variation on the pharmacokinetics (PK) of TB drugs.

2. To assess the role of genetic variation in host genes governing PK on:
   a. the efficacy of TB treatment
   b. the safety of TB treatment

3. To validate functional mechanisms for putative associations.
RAFAgene partners

University of Liverpool (UK)
(Genetic analysis)

London School of Hygiene & Tropical Medicine (UK)
(Genetic epidemiology)

National TB program (Dakar), study site

National TB program (Conakry) study site

National Hospital for TB and Pulmonary Diseases (Cotonou, Benin) study site

MRC SA (Durban, study site)

Cape Town University
(PK/ PD)
Study design and population (1)

Study participants from 2 clinical trials:

- **OFLOTUB trial** (completed)
- **RAFA trial** (ongoing)
**OFLOTUB**: To shorten TB Treatment

<table>
<thead>
<tr>
<th>Arm</th>
<th>Intensive phase</th>
<th>Continuation phase</th>
<th>Particularity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2ERHZ</td>
<td>4RH</td>
<td>6 months</td>
</tr>
<tr>
<td>2</td>
<td>2GRHZ</td>
<td>2GRH</td>
<td>4 months</td>
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Study design and population (3)

**RAFA:** To improve TB/ HIV co-infected treatment

<table>
<thead>
<tr>
<th>Arm</th>
<th>Intensive phase</th>
<th>Continuation phase</th>
<th>Particularity</th>
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<tbody>
<tr>
<td>1</td>
<td>2ERHZ</td>
<td>4RH</td>
<td>ART at 15 days</td>
</tr>
<tr>
<td>2</td>
<td>2ERHZ</td>
<td>4RH</td>
<td>ART at 2 months</td>
</tr>
<tr>
<td>3</td>
<td>2ERHZ</td>
<td>4RH</td>
<td>ART at 2 months + High R</td>
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Study design and population (4)

OFLOTUB

- 1864 TB patients recruited
- 343 in the PK study
- 575 in pharmacogenetic study

RAFA

- 1125 TB patients being recruited
- 300 in PK study
Pharmacokinetic (PK) analysis

- Serial blood samples (pre-dose and at various hours after TB treatment dosing)
- Samples processed and analyzed by liquid chromatograph mass-spectrometry (LC-MS)
- Area under the curve (AUC) measured
PK/PD outcome measures

PK outcome measures: AUC for TB drugs

PK/ PD outcome measures:

Primary Outcome measure: Unfavorable TB treatment outcome (failure / recurrence / death)

Secondary outcome measures:
- Relapse 1 year after the end of the TB treatment
- Treatment failure
- Time to TB culture conversion
- Type, frequency and severity of Adverse Drug reaction
Genetic analysis

Comprehensive approach to identify relevant genetic markers relevant to drug absorption, distribution, metabolism, and elimination (ADME):

- **Affymetrix** DMET Plus Premier Pack comprising 1936 polymorphisms in ~230 genes relevant to ADME

- **Sequenom** iPLEX platform or **real-time PCR** for a number of hypothesis-driven targeted variants in genes not covered in Affymetrix (based on litterature).
Functional validation

If association PK/PD and genetic analysis, mechanistic relevance of single nucleotide polymorphisms (SNPs) will be evaluated:

- To confirm the biological plausibility
- To help understand underlying mechanisms of identified SNP associations

A range of in vitro techniques will be employed
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<th>Capacity building (1)</th>
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<tr>
<td><strong>Senegal, Guinea</strong>: Good Laboratory Practices training</td>
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<td><strong>Benin</strong>: DNA archive establishment</td>
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<tr>
<td><strong>Benin</strong>: Implementation in Benin of <em>real time PCR</em> for genetic analysis to facilitate future genetic research studies.</td>
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### Capacity strengthening proposed

Building of a larger team with:

- Expertise in (pharmaco) genetics, epidemiology, statistical genetics and bioinformatics

- A hub in Benin through training of younger African scientists:
  
  1 PhD, 2 MSc and various courses (PK, TESA courses, genetic epidemiology)

Participation in international research meetings
Where are we?

- **Oflotub trial:**
  - Completed
  - PK/PD data available

- **Rafagene project:**
  - On-going
  - 160/300 already in PK study
Where are we?

- **Protocol:**
  - Draft available, input from NIH
  - Being circulated among partners for finalization

- **Informed consent:**
  - Draft available, being circulated
  - To be improved with aspects discussed during this meeting
Problems faced

- Delay in getting the funds leading to a delay in getting full involvement of all partners
- Already fixed
Perspectives

- Help offered by NIH:
  - Financial aspects
  - Administrative issues
  - Technical aspects
Next steps

- Finalization of the protocol/ translation in french
- Ethical clairance
- While waiting for ethical clairance:
  - Training for dedicated staff
  - Development of all SOPs
  - Ordering consumables/ reagents
Thank you