

# RAFAgene Project: Where are we?

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# Outline

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1. Overview on RAFAgene project
2. Progress to date
3. Patient recruitment and data collection
4. Challenges

# RAFAgene project?

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*Contribution of Genetic Variation to  
Pharmacokinetic Variability and Toxicity in  
Patients Undergoing Multi-drug Tuberculosis  
Treatment in Sub-Saharan Africa*

# Background

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## Tuberculosis (TB):

- Important cause of death in Sub-Saharan Africa
- In best-case of TB treatment scenario, **≈ 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

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– To conduct :

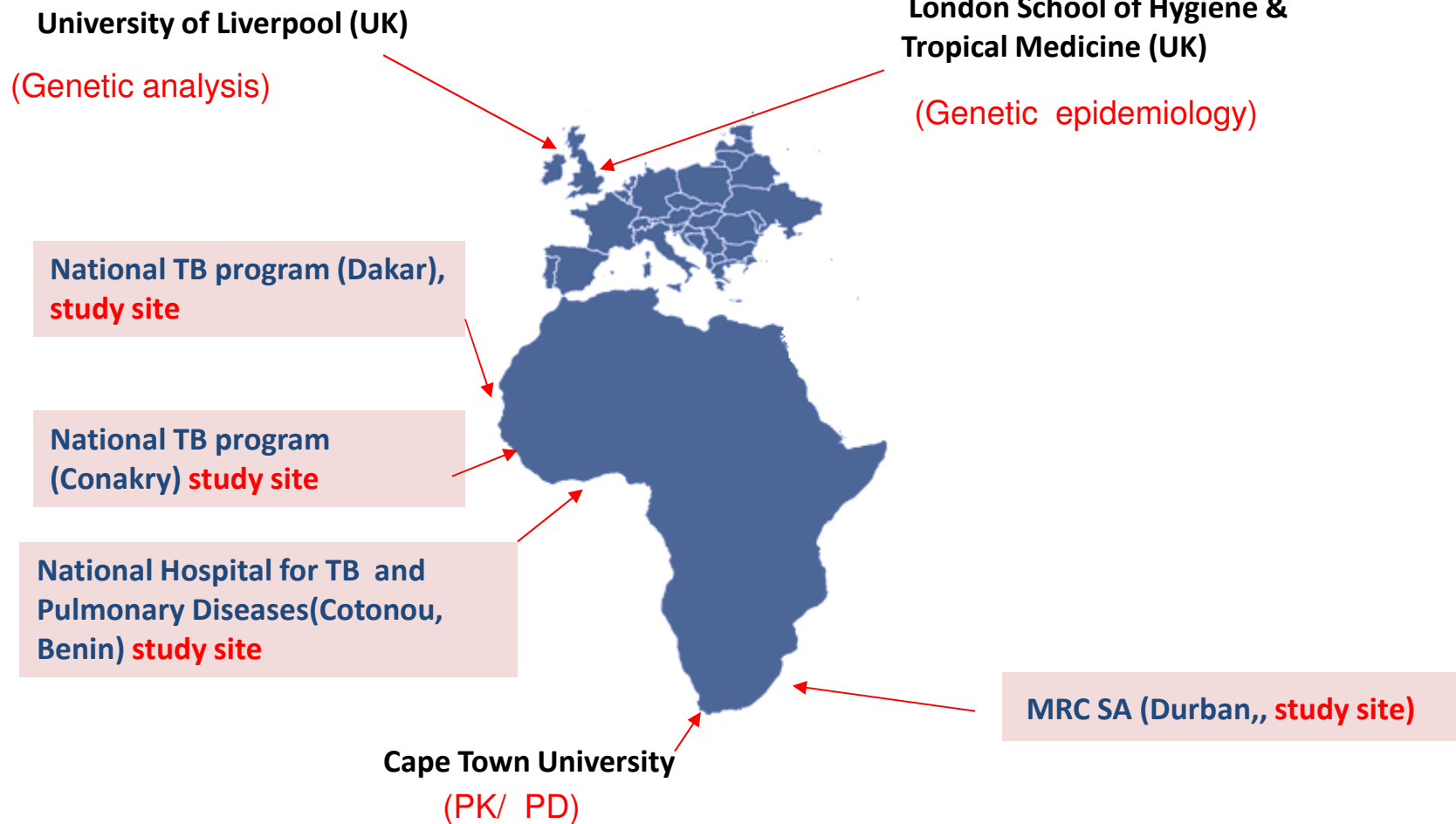
- a pharmacogenetic study
- of TB drugs (Rifampicin, Isoniazid, Ethambutol, Pyrazinamide and Gatifloxacin)
- in TB patients in Sub-Saharan Africa

# Specific aims

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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 the efficacy and safety** of TB treatment
3. To validate **functional mechanisms** for putative associations.
4. To strengthen pharmaco(genetic) **research capacities** in Africa

# RAFAgene partners



# Study design and population (1)

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**Study participants from 2 clinical trials:**

– *OFLOTUB trial (completed)*

– *RAFA trial (ongoing)*



# Study design and population (2)

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**OFLOTUB**: To shorten TB Treatment

Arm	Intensive phase	Continuation phase	Particularity
1	2ERHZ	4RH	6 months
2	2GRHZ	2GRH	4 months

ORIGINAL ARTICLE

## A Four-Month Gatifloxacin-Containing Regimen for Treating Tuberculosis

Corinne S. Merle, M.D., Katherine Fielding, Ph.D., Omou Bah Sow, M.D., Martin Gninafon, M.D., Mame B. Lo, M.D., Thuli Mthiyane, M.Sc., Joseph Odhiambo, M.D., Evans Amukoye, M.D., Boubacar Bah, M.D., Ferdinand Kassa, M.D., Alimatou N'Diaye, M.D., Roxana Rustomjee, M.D., Bouke C. de Jong, M.D., Ph.D., John Horton, M.D., Christian Perronne, M.D., Charalambos Sismanidis, Ph.D., Olivier Lapujade, B.Sc., Piero L. Olliaro, M.D., Ph.D., and Christian Lienhardt, M.D., Ph.D., for the OFLOTUB/Gatifloxacin for Tuberculosis Project\*

ABSTRACT

*Corinne S. Merle et al. A Four-Month Gatifloxacin-Containing Regimen for Treating*

*Tuberculosis. N Engl J Med 2014; 371:1588-1598/*[October 23, 2014](#)*/DOI: 10.1056/NEJMoa1315817*

# Study design and population (3)

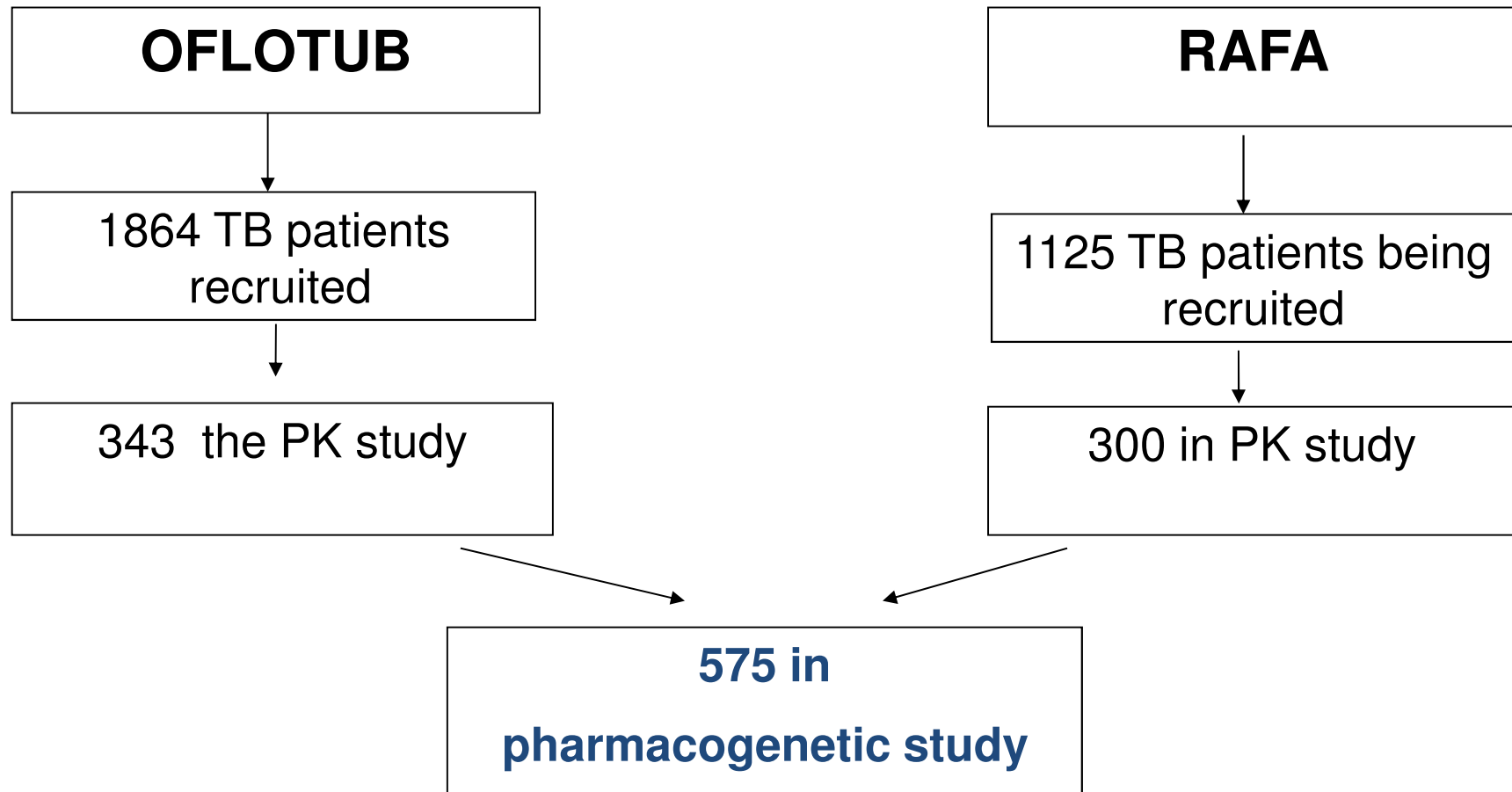
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**RAFA**: To improve TB/ HIV co-infected treatment

Arm	Intensive phase	Continuation phase	Particularity
<b>1</b>	2ERHZ	4RH	ART at 15 days
<b>2</b>	2ERHZ	4RH	ART at 2 months
<b>3</b>	2ERHZ	4RH	ART at 2 months + High R

# Study design and population (4)

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# Pharmacokinetic (PK) analysis

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- 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

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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
- Time to TB culture conversion
- Type, frequency and severity of Adverse Drug reactions

# Genetic analysis

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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 Affimetrix (based on literature).

# Functional validation

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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



# Capacity building (1)

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**Senegal, Guinea: Good Laboratory Practices training**

**Benin: DNA archive establishment**

**Benin:** Implementation in Benin of **real time PCR** for genetic analysis to facilitate future genetic research studies.

## Capacity building (2)

### Capacity strengthening

Building of a large team with:

- Expertise in (pharmaco) genetics, epidemiology, statistical genetics and bioinformatics
- A hub in Benin through training of younger African scientists: **1 PhD, 3 MSc and various courses (PK, TESA courses, genetic epidemiology)**

# Progress to date

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- Date of start: August 2012
- Years 1 and 2
  - Study documents made available in French and English version
  - Protocol submitted to ethical committees
    - *Ethical approval in Benin, Senegal, Guinea, Cape Town*
    - *Durban: process ongoing, hopefully before December*
  - Participants already traced on each study site  
(updated address, phone numbers and calls)

# Recruitment process

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- Benin: Recruitment ongoing (116 participants)
- Senegal: very soon (hopefully this month)
- South Africa: as soon we get Ethics Approval
- Guinea: not yet (EBOLA++++)

# Timeline

- Year 3 of the project started in August 2014

# Initial Project management plan

Year 1	<b>M0 to M6:</b> Elaboration of the study documents (protocol, IC, work-plan) Submission to the ethical committees, Set-up of the study in each study site Training on study procedures of study staff
	<b>M6 to M12:</b> Tracing and blood sampling of the PK patients of the OFLOTUB trial. Prospective inclusion of the PK patients from the RAFA trial.
Year 2	<b>M0 to M6:</b> End of recruitment and sampling of the PK patients of the RAFA trial.
	<b>M6 to M12:</b> Start of the PK analysis and the genetic analysis (screening using the Affymetrix DMET Plus Premier Pack)
Year 3-4	<b>M0 to M12:</b> Continuation of genetic analysis and start of the Population PK modeling
Year 5	<b>M0 to M10:</b> Further genetic analysis carried out (in particular in vitro analysis) Continuation of the Population PK modelling
	<b>M11 &amp; M12:</b> Finalisation of the study report and publications

# Challenges

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- NIH new procedures
- Ethical approval: at least 06-12 months
  - *It was tough to convince the EC to give us approval to use dead patients samples to perform the genetic analysis*
- Delay of activities in Guinea (EBOLA outbreak)
  - *Back up plan: to use the PK samples for genetic analysis?*

# Conclusion

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- Project ongoing
- One year late on the initial plan
- Ebola outbreak in Guinea!!!



# Ebola outbreak: a major obstacle for patient care and research

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- Because of Ebola, we are not doing exactly what we planned for RAFAgene
- Because of Ebola, Liberia, Sierra Leone are not doing what they planned/expected
- Because of Ebola, more deaths would occur from other diseases (simple malaria, dehydration, anemia....) than Ebola itself. Why?
- Because people are no longer going to the health facilities, or even if they go there, there is nobody to care of them (HW are running away)
- Let us do something!!!!

**Thank you**