PROTOCOL & INFORMED CONSENT

TITLE: "Study of TB lesions obtained in surgery: in search of best biomarkers correlating with TB pathology, clinical features, MDR cases and prognosis"

Acronym: SH-TBL (Study of Human TB Lesions).

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1. STATE OF ART AND RATIONALE

Nowadays, Tuberculosis (TB) is still an international public health problem, in spite of existing an effective treatment. Every year, 9 million people get sick and 1 million of them die. Recently, one of the major problems for health systems (in terms of both medical aspect and budget) of all countries are those cases due to Multi-Resistant to Drugs strains (MDR-TB), which represented up to half a million last year. The average length of hospital stay and duration of treatment are increasing due to MDR-TB cases, with an associated increasing burden on National TB Control Programmes. Moreover, these cases have poor treatment outcomes associated and

In Spain, tuberculosis is not a big problem, and yet during 2013 we had 5539 notified cases and an incidence of 13 cases per 100.000 people is estimated. However, due to our national history of fight against the disease, we have one of the most skilled scientific network at international level in TB research field, the Experimental Tuberculosis Unit (Unitat de Tuberculosi Experimental, UTE) being a renown reference in Europe.

In this context, new approaches to ameliorate the response to TB treatment are a priority; especially those aiming to reduce morbidity, mortality and treatment duration, all taking into account the MDR-TB cases. Moreover, these new options are required to be worldwide available, to be used immediately and for any patient, implying them needed to be cheap.

During the last 20 years, a lot of progress has been made in the design and development of new drug and vaccine candidates, but this is a hard, time and cost-consuming activity with low or none output at short-term and doubtful output at long-term either (only one out of 10.000 new compounds will arrive to the market and only after 15 years of a rigorous pre-clinical and clinical development).

Meanwhile, physicians deal with clinical TB management based on old premises, most of them strictly clinical and empiric approaches, and the TB drug pipeline stills remains sparse.

Nowadays in TB, there is any protector correlator, diagnose or prognosis biomarker known. International scientific community dedicated to TB field is focused to find it, and for this reason many resources are dedicated. During the last years, different genetic profiles has been found in peripheral blood related with TB disease, pointing that this genetic signatures involving more than one parameter could establish the key of futures therapeutic approaches. However, the same authors of these projects specify that it is necessary to check, compare and validate these

results with the genetic profiles found in the TB lesions. In our opinion these data would be not necessarily equal but complementary which would explain the reason of the disease generation in some infected patients and not in others, the different prognostic for distinct patients, the role of inflammation in the disease and infection progression and the response to treatments and vaccines. Moreover, they will provide robustness and parameter restriction to the profiles found in blood. For a further commercial exploitation, it is better a profile with 3 common characters in blood and lesion than 10 parameters in blood. However, the reason why the researches use peripheral blood instead of samples of lesions in these studies is only due to the availability of samples. The majority of top countries in TB research works in collaboration with African countries which have high incidence of TB and also have a high rate of coinfection with HIV masking and difficult works like ours, in which the histopathology is very important. On the other hand, after an age when surgery was a common treatment in Europe and America this technique was no longer necessary after the emergence of anti-TB drugs in the 50's and they fell into disuse. Nowadays, almost any neither European nor American physician has the experience in this type of practice. However the irruption of drug multiresistant strains has changed the landscape. Asia, and especially Eastern countries (with exURSS countries in lead) have a high number of MDR cases and still very high rates of TB. Georgia is one of these countries. It has an incidence 10 times higher than Spain, a low rate of HIV-coinfection and they are still obligated to operate their TB patients, because more than a half are MDR and fails to the standard treatment.

NCTLD is the reference center in Georgia dedicated entirely to TB and with highly expert surgeons in clinics and surgery of TB lesions and yet, without any or few experience on research. Dr. Vilaplana and her team are experts of basic research of the disease; they have been involved in all aspects of TB research like developing and evaluating vaccines and new therapies; and also immunology in clinical trials and pathology of lesions in experimental animal models. This created association is based in professional loyalty between these two teams ensures the creation of a unique international collection, that after being exploited by the two teams will generate an information that can be used in collaboration with other leading international groups to ensure a translation and exploitation of obtained results.

2. AIM

To perform a genetic, protein and microbiological analysis on a unique collection of biological samples of TB patients (sensitive and MDR-cases).

3. HYPOTHESIS

The correlation of the morphologic, microbiological, genetic and histopathological characteristics of TB lesions obtained in therapeutical surgery with the clinical forms and features of the patients will provide essential information

a) on the role of the host in the mechanisms associated to the generation and evolution of active TB and

b) about future diagnostic and/or prognostic biomarkers of TB disease.

All this information could be used for patients stratification and/or to design new therapeutic strategies.

4. SPECIFIC OBJECTIVES

To achieve the general aim of the project, we plan to achieve 2 specific objectives:

3.1. Description study of the morpho-histopathological characteristics of TB lesions and its correlation with the clínico-pathological features of TB patients who underwent therapeutical surgery during 2014-2016. The aim of this objective is to conduct a descriptive study to know about the characteristics of TB patients which need therapeutical surgery, and to evaluate its impacto on patients' morbility and mortality.

3.2. Prospective study of the TB lesions obtained in therapeutical chest surgery. The aim of this objective is to obtain a genic-proteomic profile of in tissues which correlate to the histopathology of the granulomas and/or the clinic-pathological features of TB patients.

5. M&M

1. Study design

The project is part of a collaboration agreement between the UTE and the NCTLD, and already obtained the Ethics Committee approval (IRB00007705 NCTLD Georgia #1, IORG0006411). The protocol approved includes lesions' collection during therapeutical surgery, as well as the collection of demographic data, clinical features and analytical data of the patients included in the study, data on their evolution pre and post-surgery, complications and survival. The data

collection is done in the Georgian center supervised by the NCTLD team and coordinated by the IP, Dr Vilaplana, and the samples and data will be shipped to the UTE for their analysis in collaboration with the Georgian team.

The project is an observational study including 2 substudies:

1. Description study of the morpho-histopathological characteristics of TB lesions and its correlation with the clínico-pathological features of TB" (Objective 1). Data on patients (all cases, both DS and MDR/XDR-TB) therapeutically operated an their lesions during an initial period 2014-2016 will be retrospectively recorded in a spreadsheet file from the surgical notebooks in an anonimized way.
2. For the "Prospective study of the TB lesions obtained in therapeutical chest surgery" (Objective 2): Clinical and epidemiological data and tissue, blood and urine samples will be anonymously collected from patients submitted to therapeutical surgery.

2. Study population and eligibility

Study Population

Patients undergoing therapeutic surgery for their Pulmonary Tuberculosis at NCTLD in Tbilisi, Georgia.

- For Description study of the morpho-histopathological characteristics of TB lesions and its correlation with the clínico-pathological features of TB" (Objective 1): Data on patients (all cases, both DS and MDR/XDR-TB) therapeutically operated an their lesions during an initial period 2014-2016 will be retrospectively recorded in a spreadsheet file from the surgical notebooks in an anonimized way.
- For the "Prospective study of the TB lesions obtained in therapeutical chest surgery" (Objective 2):

Eligibility:

Inclusion Criteria:

- Patients of all ages and sexes undergoing therapeutical surgery for their Pulmonary Tuberculosis at NCTLD in Tbilisi, Georgia indicated as per clinical routine

Exclusion Criteria:

- Non consenting to donate samples and/or data for the study

6. Ethics:

The project protocol and associated documents was reviewed and approved by both the ethics committee of the NCTLD (IRB00007705 NCTLD Georgia #1, IORG0006411) and the Germans Trias i Pujol Research Institute (IGTP) ethics committee (EC: PI-16-171).

In the retrospective study, the patients included underwent surgery during the past 2-5 years time, and they already filled in the Informed Consent for the surgery. In this study, only the epidemiological and clinical data of the patients will be collected in an anonymized way together with the histopathological data from the lesions obtained. No extra samples or data are needed for this substudy, thus no extra Informed Consent will be needed.

For the prospective substudy, an informed consent (attached as Annex 3) will be obtained for the collection of biological material and data from all study participants before they were enrolled.

Each patient will be given a sequential number coded as SH-TBL XXX (XXX meaning the correspondent number of patient).

For each patient, a non anonymized form created ad-hoc for this project will correlate him/her with his/her projects' code. This form will be to be kept together with the Medical Record of each patient as the Hospital Records copy. A spreadsheet file will be filled-in with the following data of each patient included: name, the Hospital Record Number and the correspondent Project's code (SH-TBL XXX). Another form created ad-hoc will be filled-in for each patient included. In order to comply with the patients' rights of confidentiality, this form will be anonymized, without the name and surnames of the patient and where only the project's code will be recorded, together with all the clinical data associated to the specific case. A spreadsheet file will be filled-in with the following data of each patient included: Project's code (SH-TBL XXX), clinical characteristics, characteristics of the lesion to be removed, and monitoring data. In order to comply with the ethics requirements of samples' collections, both spreadsheets will be kept as 2 different documents and stored in 2 different computers.

All studies will be conducted blindly.

7. Parameters and measurements

There are 2 cohorts/study groups, each corresponding to one of the substudies, with different outcome measures and parameters:

4.2.1. FOR THE "DESCRIPTION STUDY OF THE MORPHO-HISTOPATHOLOGICAL CHARACTERISTICS OF TB LESIONS AND ITS CORRELATION WITH THE CLINICO-PATHOLOGICAL FEATURES OF TB" (OBJECTIVE 1):

Retrospective cohort.

Primary Outcome Measures:

• Description of Clinical and Epidemiological Data of the TB patients enrolled. Time Frame: at baseline. Descriptive analysis; data recorded in a spreadsheet created ad-hoc.

•Description of the Histopathological characteristics of the TB lesions of TB patients enrolled. Time Frame: at baseline. Descriptive analysis; data recorded in a spreadsheet created ad-hoc

From surgical notebooks of TB patients submitted to therapeutical surgery the following data will be recorded (anonymously) in a spreadsheet file:

Patients' data (epidemiological and clinical data):

- Sex
- Age
- Smoking and alcohol intake habits
- Comorbilities: diabetes, immunosuppression, HIV-coinfection, renal disease, COPD, others
- TB form: pulmonary, extrapulmonary, pulmonary+extrapulmonary, disseminated
- Type of TB according to drug sensitivity (WHO definitions)
- History of previous treatment
- Anatomical site of TB
- Date of TB diagnosis
- Date of Treatment initiation
- number of lesions found in radiology assays

- Bacteriology cured? (WHO definitions)
- Time of negativization of culture (in months)
- Indication for surgery, main reason
- Number of lesions operated
- Type of surgery done
- Date of surgery
- Post-surgery complications
- Final outcome (WHO definitions)
- Date of death if appropriate

For each lesion operated:

- Type of lesion
- Presence of fibrosis/cirrhosis
- Size (mm)
- picture

Work plan and estimated calendar:

Data will be recorded during the first year (ideally during the first 6 months), and the analysis and reporting done during the second year of the project.

Statistics

Data obtained will be described (descriptive analysis) but also statistically analyzed by multivariant analysis with the aim to find correlations between the different variables included and to identify the factors which might have an impact on the final outcome.

4.2. FOR THE "PROSPECTIVE STUDY OF THE TB LESIONS OBTAINED IN THERAPEUTICAL CHEST SURGERY" (OBJECTIVE 2):

Prospective cohort: data and samples will be prospectively included from TB patients undergoing therapeutical surgery (DS- and MDR/XDR-TB). Data will be recorded in an

electronic form which has been already created ad-hoc (ElectronicDataCapture, Clincapture, Clinovo, http://www.clinovo.com/products/clincapture). In this form, we have included: clinical and epidemiological data of patients; data on collection and process of biological samples; Health Quality of Life (HQoL) questionnaires data.

Primary Outcome Measures:

• Description of Clinical and Epidemiological Data of the TB patients enrolled. Time Frame: at baseline. Descriptive analysis; data recorded in a spreadsheet created ad-hoc.

•Description of the Histopathological characteristics of the TB lesions of TB patients enrolled. Time Frame: at baseline. Descriptive analysis; data recorded in a spreadsheet created ad-hoc

•Obtention of a genic-proteomic profile of TB lesions tissues which correlate to the histopathology of the granulomas and/or the clinic-pathological features of TB patients. Time Frame: at baseline. Descriptive analysis, correlation with histopathological characteristics of TB lesions and with clinical and epidemiological data of TB patients

Secondary Outcome Measures

•Change in Immunological responses. Time Frame: at baseline; and at the moment of discharge, an average of at day 15 post-enrollment. Immunological responses will be measured 2.1.3. Identification of biomarkers in blood at protein level in blood and urine; validation in tissue and blood of genic biomarkers secreted (ELISA, qPCR, immunohistochemistry).

•Change in Health Quality of Life Measurements. Time Frame: at baseline (before surgery) and through study completion, an average of 1 year. Measured with Health Quality of Life Questionnaires.

Data will be recorded in an electronic form which has been already created ad-hoc (ElectronicDataCapture, Clincapture, Clinovo, http://www.clinovo.com/products/clincapture). In this form, the following data will be collected:

- Epidemiological and clinical data will be collected from all patients at baseline (prior surgery).
- Health Quality of Life (HQoL) questionnaires: SGUL's Respiratory Questionnaire, Kessler-10 and BCN-Q will be used to evaluate the social and psychological factors associated to the patients included in the study. The patients will be reevaluated at the moment of discharge and during the follow-up if they are scheduled as per routine.

The following samples will be prospectively collected from patients undergoing therapeutic surgery and enrolled in the prospective substudy:

- Tissue samples from the TB lesions
- Blood samples for plasma obtention and whole blood for RNA studies
- urine

During surgery, the following tissue samples from the following areas of the removed lesions will be collected:

1. cavity center
2. cavity internal wall
3. cavity external wall
4. nearby visually healthy tissue around the cavity

If a TB lesion (nodulus) is detected, samples of it will also be collected.

These samples will be used for 1) the genetic and proteomic studies; 2) histopathology; 3) microbiologic studies. For histopathological analysis a single piece including the 4 areas of the granulomas will be collected. For genetic and proteomic and microbiological studies, individual samples will be collected from each area.

If there will be no possibility to collect 3 samples of each zone for these 3 purposes, then the priority will be 1st: samples for genetic and proteomic studies; 2nd: samples for microbiology and 3rd: samples for histopathology.

A protocol for collecting and processing patient's tissue samples has been attached as Annex 1.

Blood sample for plasma (in a 10mL EDTA tube) and whole blood for RNA studies (in a 2,5mL PaxGene RNA tube) plus a urine sample will be collected prior to surgery (baseline) and at the moment of clinical discharge. Extra-samples will be collected in next post-surgery follow-up visit if possible (as indicated by clinical management routine). A protocol for processing blood and urine samples has been attached as Annex 2.

Samples collected will be stored to perform the planned studies and the remaining samples will be kept for further studies if considered appropriate by the PI and according to extra-funding

possibilities. All samples collected will be recorded and labeled according to a specific code for the present project (SH-TBL plus the number correspondent to the patient's number).

8. RELEVANT BIBLIOGRAPHY

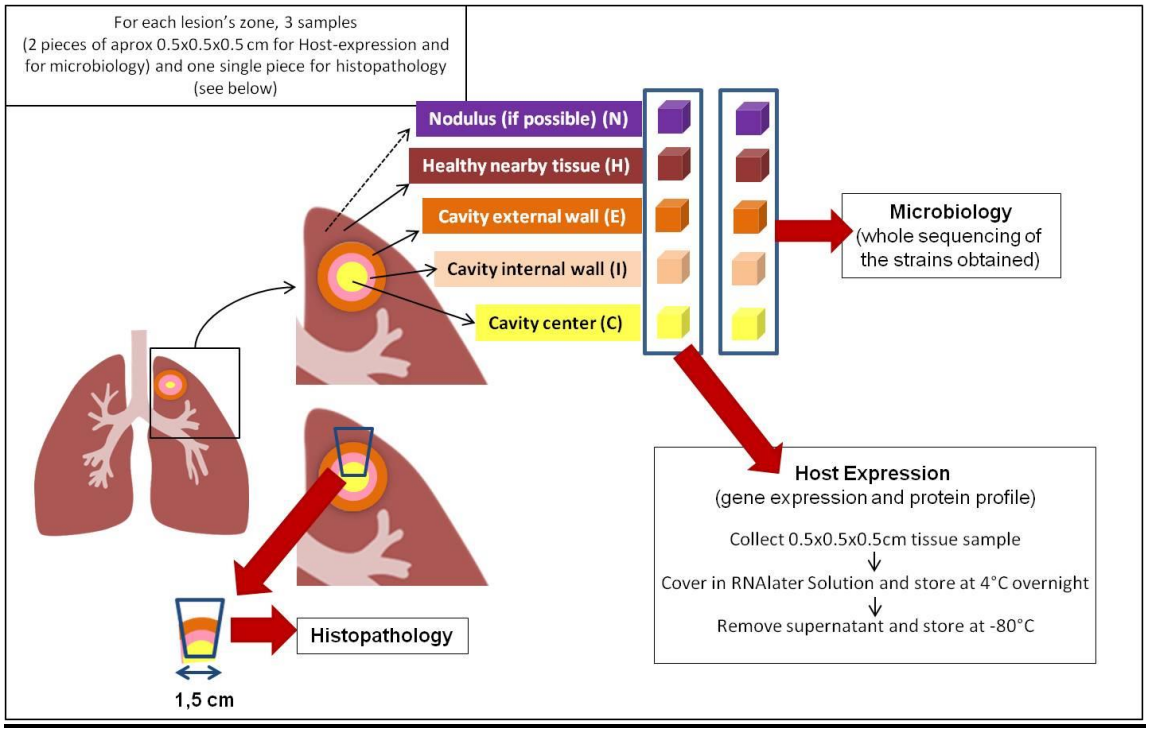
1. Who. Global tuberculosis report 2015 (WHO/HTM/TB/2015). 2014; Available from: http://apps.who.int/iris/bitstream/10665/191102/1/9789241565059_eng.pdf?ua=1
2. World Health Organization. WHO Tuberculosis country profiles [Internet]. 2015 [cited 2015 Sep 30]. Available from: http://www.who.int/tb/country/data/profiles/en/
3. Zumla A, Maeurer M. Rational development of adjunct immune-based therapies for drug-resistant tuberculosis: Hypotheses and experimental designs. J Infect Dis. 2012;205(Suppl 2):335–9.
4. Schito M, Migliori GB, Fletcher HA, Mcnerney R, Centis R, D 'ambrosio L, et al. Perspectives on Advances in Tuberculosis Diagnostics, Drugs, and Vaccines. Clin Infect Dis. 2015 Oct 15;61Suppl 3:S102-18. doi: 10.1093/cid/civ609.
5. Berry MPR, Graham CM, Mcnab FW, Xu Z, Bloch SAA, Oni T, et al. An Interferon-Inducible Neutrophil-Driven Blood Transcriptional Signature in Human Tuberculosis.
6. Kaufmann SHE, Lange C, Rao M, Balaji KN, Lotze M, Schito M, et al. Progress in tuberculosis vaccine development and host-directed therapies-a state of the art review. Lancet Respir Med [Internet]. Elsevier Ltd; 2014;2(14):301–20. Available from: http://dx.doi.org/10.1016/S2213-2600(14)70033-5
7. Anderson ST, Kaforou M, Brent AJ, Wright VJ, Banwell CM, Chagaluka G, et al. Diagnosis of Childhood Tuberculosis and Host RNA Expression in Africa. N Engl J Med. 2014;370:1712–23.
8. Maertzdorf J, Ota M, Repsilber D, Mollenkopf HJ, Weiner J, Hill PC, et al. Functional correlations of pathogenesis-driven gene expression signatures in tuberculosis. PLoS One. 2011;6(10):e26938. doi: 10.1371/journal.pone.0026938. Epub 2011 Oct 28.
9. Zumla A, Abubakar I, Raviglione M, Hoelscher M, Ditiu L, McHugh TD, et al. Drug-Resistant tuberculosis-current dilemmas, unanswered questions, challenges, and priority needs. J Infect Dis. 2012;205(Suppl 2).
10. Dara M, Sotgiu G, Zaleskis R, Migliori GB. Untreatable tuberculosis: is surgery the answer? Eur Respir J. 2015 Mar;45(3):577-82. doi: 10.1183/09031936.00229514.
11. Madansein R, Parida S, Padayatchi N, Singh N, Master I, Naidu K, Zumla A, Maeurer M. Surgical treatment of complications of pulmonary tuberculosis, including drug-resistant tuberculosis. Int J Infect Dis. 2015 Mar;32:61-7. doi: 10.1016/j.ijid.2015.01.019.

9. ANNEX 1. PATIENT'S TISSUE SAMPLES TO BE COLLECTED WITHIN THE PROSPECTIVE SUBSTUDY

For each patient, and lesion removed, samples of the removed lesions should be obtained and labeled with the patient's code, the data of collection, the zone of obtention and the purpose according to the following premises:

ZONE OF OBTENTION	CODE
cavity center	C
cavity internal wall	I
cavity internal wall	E
visually healthy tissue around the cavity	H
nodulus	N

PURPOSE	CODE	NUMBER OF SAMPLES TO BE COLLECTED
Samples for gene expression and protein profile (Host expression)	HExp	1 per each zone
Microbiology	Mic	1 per each zone
histopathology	Path	1 single piece with all zones



Samples for gene expression and protein profile

1. Do not freeze tissues before immersion in RNAlater Solution.
2. Cut large tissue samples to ≤0.5 cm in any single dimension.
3. Place the fresh tissue in 5–10 volumes of RNAlater Solution in a properly labeled criotube.
4. Do not freeze samples in RNAlater Solution immediately; store at 4°C overnight (to allow the solution to thoroughly penetrate the tissue), remove supernatant, then move to –80°C for long-term storage.

Samples for histopathology

Samples will be collected as one single piece including the different parts of granuloma, and should be fixed processed in 10% buffered formalin and sent to the UTE for it's histopathology analysis.

Samples for microbiology:

The principal aim is to obtain *M.tuberculosis* isolates for further characterization (whole sequencing).

If there is limited quantity of biological material, sampling for genetic and proteomic studies shall be prioritized and the volume of samples collected for microbiology and histopathology could be reduced (always expressing it as incidence in the samples collection form).

10. ANNEX 2. PROTOCOL TO PROCESS PATIENT'S BLOOD AND URINE SAMPLES

For the samples' quality, keep on ice or at the fridge (<4ºC) until they are processed, which should be done in less than 1 hour after their extraction. Labels: each microtube should be labeled with the patient's code and the date it was obtained.

For serum collection:

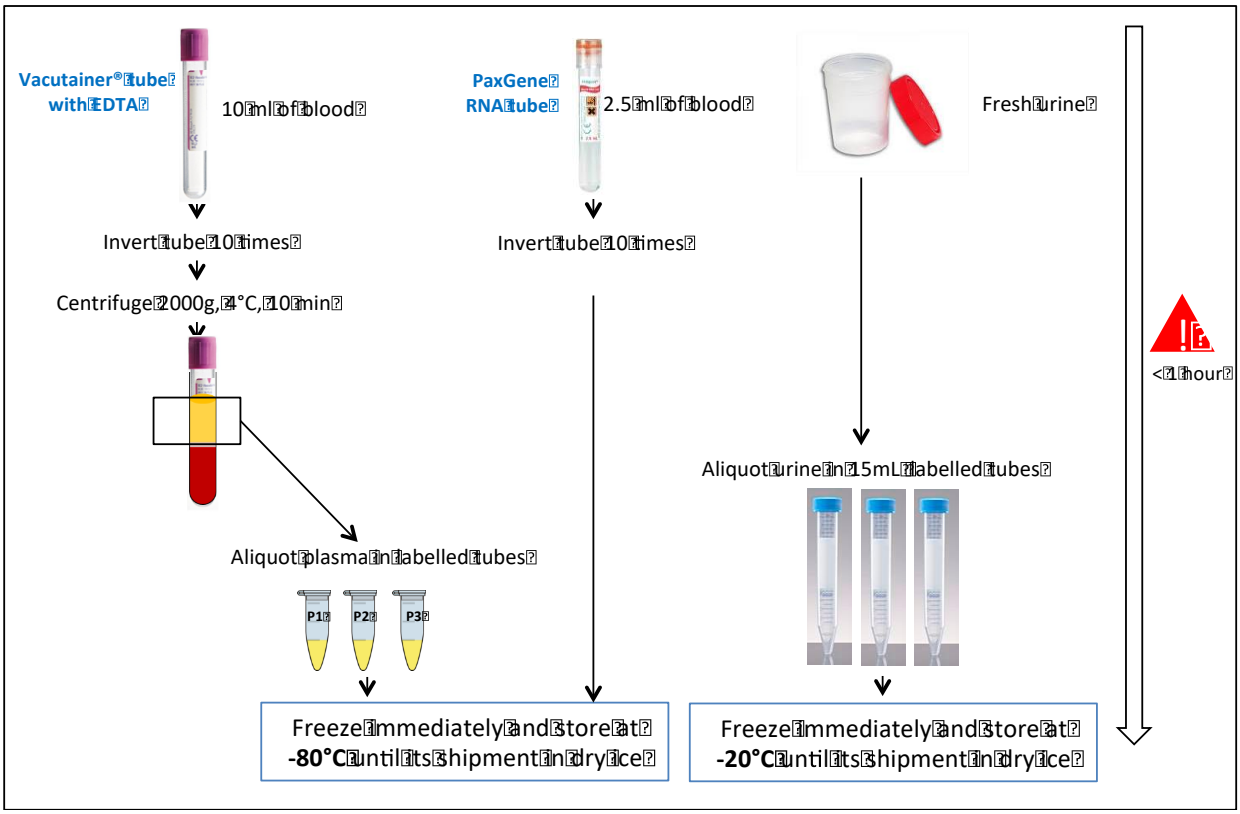
1. Extract 10 ml of blood in tubes with EDTA (anticoagulant). It should be attempted to perform the blood extraction at the same time as a routine blood test.
2. Invert the tube 10 times to mix the anticoagulant with blood (do not shake).
3. Immediately after, centrifuge at 2000g and 4°C for 10 minutes (if it's not possible to do it immediately after, maintain the sample at 4°C in ice or otherwise in 4°C water).
4. Isolate the plasma (approx. 3 ml) right after the centrifugation (avoid over half an hour elapse) and aliquot in 2-3 properly labeled microtubes (patient's code number, date, the letter "P" for plasma and the tube number).
5. Store immediately the plasma at 80°C until its shipment.

For whole blood collection for RNA:

1. Extract 2,5 ml of blood into PAXgene Blood RNA Tubes properly labeled (patient's code number, date, and the tube number). It should be attempted to perform the blood extraction at the same time as a routine blood test.
2. Invert the tube 10 times (do not shake) and store immediately at -80ºC until its shipment.

For urine collection:

1. Collect urine samples in the collection tube and aliquote it in properly labeled 15mL tubes (maximum 10mL of urine per tube), properly labeled with patient's code number, date, the letter "U" for urine and the tube number. Store immediately at -20ºC until its shipment.


Vacutainer® tube with EDTA
10 ml of blood
PaxGene RNA tube
2.5 ml of blood
Fresh urine
Invert tube 10 times
Invert tube 10 times
Centrifuge 2000g, 4°C, 10 min
< 1 hour
Aliquot plasma in labelled tubes
P1
P2
P3
Aliquot urine in 15mL labelled tubes
Freeze immediately and store at -80°C until its shipment in dry ice
Freeze immediately and store at -20°C until its shipment in dry ice

11. ANNEX 3. INFORMED CONSENT FORM

INFORMED CONSENT SHEET

This data sheet may contain terms that you don´t understand. Do not hesitate to ask your doctor or the attending personal any questions that you may have.

Title: "Study of TB lesions obtained in surgery: in search of best biomarkers correlating with TB pathology, clinical features, MDR cases and prognostic: SH-TBL (Study of Human TB Lesions)."

We are writing to inform you about a research study we would like you to join. The study was approved by the Clinical Research Ethics Committee of the National Center for Tuberculosis and Lung Diseases (NCTLD) and is conducted according all the current European Laws on Ethical Research.

Our intention is just to provide you with the correct and necessary information to help you consider and decide if you want to participate or not. For this, we are asking you to read this information carefully. The study's doctor will clarify any doubts you may have after reading the explanation.

The aim of this document is to offer you information in order you can decide if you want to hand us your biological samples exclusively with research purposes, in the way we will explain you below. The biological samples consist in one/two blood sample(s) plus tissue samples of the extracted lesion for which you will be operated. To conduct the present Project we do expect to collect biological samples from approximately 100 patients having had surgery in the NCTLD within a year.

Why is this study taking place?

Tuberculosis is still an important problem around the world. Every year 100 million people acquire this infection. Its prevention is currently very difficult, since this is a disease caused by an airborne bacterium (*Mycobacterium tuberculosis*). Of all people getting infected, only some will develop the disease and, to this date, we still don´t know

why some people get sick and why other's don´t. Georgia has a high burden of people ill from tuberculosis (TB), half of them being due to bacilli resistant to common therapies, and for this reason its physicians and surgeons are experts on TB management. A research team from Barcelona (Catalonia, Spain) leaded by Dr Vilaplana and in collaboration with the surgery team of the NCTLD headed by Dr. Vashakidze and the microbiology team of the same institute (Dr. Shubladze) want to study the TB lesions removed within routine surgery of this disease in order to 1) understand the mechanisms of disease generation; 2) find new therapies and 3) find new diagnostic methods to stratify TB patients. The final aim of the study is to better address and manage the patients' disease.

What will you have to do in this study?

You have been approached because you will be surgically intervened for your condition.

If you do accept to participate, we will use the lesion removed to perform our studies.

This will not modify any procedure from the prescribed routine designed by your surgeon. This will not represent any added procedure to your clinical management plan but an extra blood sample collection.

The study consists of using the tissue sample removed within routine surgery of your disease and 2 blood samples (one prior to surgery and another during follow-up visit).The samples will be kept in the Experimental Tuberculosis Unit lab (person in charge: Dr. Cristina Vilaplana) and will be handled according to the Biomedical Research Law 14/2007. They will be labeled with the study's research code (a numeric one that does not identify you directly), and they will only be used for the study's purposes and they will be kept during 10 years for future research related to the disease and previously approved by an Ethics Committee.

The results will be introduced in a database and will be used for scientific purposes, and the data will always be handled by specialized personnel.

Which are the benefits, risks and alternatives to participate in this study?

The participation in this study is voluntary, and if you are not willing to collaborate in it, this will not represent any harm for you.

Your participation in this study won´t change the treatment you are receiving right now for your condition.

If you do not participate in this study, you will still receive the more appropriate treatment for your condition, as if you would during the participation. Your participation will not modify any procedure from the prescribed routine designed by your surgeon. This will not represent any added procedure to your clinical management plan but an extra blood sample collection.

As no intervention will be given to you besides the routine schedule to manage your condition, no potential side effects are expected from this study. Blood collections can cause local discomfort or bruises in the puncture area.

It is not expected that you will have a particular benefit from this study. Your participation in this study will have no cost for you and you are not going to receive any economic reward or any other kind of reward for participating.

In any case, your participation in this study may be of great help to understand your disease and may contribute to design better diagnostic and therapeutic approaches from which other patients might benefit in a short future.

Do you have to remain in the study?

Your participation is voluntary. If you do not want to participate in the study, tell the study's doctor. At any time you can decide not to continue without giving any reason for it. If you don´t want to participate in the study or if you leave the study, you will be treated as usual.

If you decide to stop participating in this study, please contact the study's physician.

All data and samples collected before your withdrawal from the study will be used for the purposes of the study.

Even if you are not interested in participating in the study anymore, your health information is very important for this study. We will ask you to let us gather information about your health till the completion of the study. For this reason, and with your permission, we would be in contact with you or, if it was not possible, with your relatives, friends or your physician. We will ask for the relevant contact information in your case.

What happens with your personal data?

The data will be coded to preserve your identity, according to the Organic

Spanish Law 15/1999 from December 13th, devoted to personal data protection. According to this law you have the right to access, change, oppose and cancel your data. To do any of these you must contact your study's physician. You can rest assured that your clinical history information will be strictly confidential and your identity will be kept anonymous.

When you will accept to participate, a code will be generated and be used to match your samples with your clinical data without need to use your personal data. Only the people responsible of this study (principal investigator and investigator team) will have access to these data if necessary. Your identity will not be revealed to anybody except when required by medical emergencies or legal requests.

Your identity will remain confidential even if some results of the study are published.

This research study will not generate any data directly applicable to you regarding your condition, as the value of the results obtained is expected at long-term.

Questions and Answers:

If you have any question or doubt related to this study please contact your physician.

INFORMED CONSENT FORM FOR SAMPLES' DONATION

Systematic collection of blood and tissue samples for the study of Tuberculosis

Patient's code number: _____

I _____ (complete name)

…have read the information sheet that was given to me
…have been able to make inquiries about the study
…have received enough information about the study
…understand that my participation is voluntary
…understand that I can withdraw myself from the study:

1. Whenever I want
2. Without giving any explanations
3. Without it affecting my medical care

For which I hereby consent that the samples obtained during my attention care may be stored and used in medical research authorized by the ethics' committee and preserving the anonymity.

Date and place: _____

Signature: _____