R&D Pipelines

The need behind

Precision Medicine is the current major trend to maximize the opportunity in chronic conditions of saving lives and improving quality of life. This means that days of "one drug to cure all" are over, instead, human diversity responses must be considered. Different patients need different drugs, and this is the driver of new medical management.

Chronic inflammation is the "poor sister" of the big human diseases family. Infectious diseases, cancer and many others now have been managed under precision medicine protocols for decades. Culture + antibiograms are mandatory to prescribe antibiotics, and nowadays nobody thinks of cancer treatment without biomarker targeted therapies. On the contrary, chronic inflammation remains treated with immunosuppressant drugs mostly based on clinical guidelines, drug blood levels and trial/error approaches.

Inflammatory diseases are clearly lacking a tool to determine the potency (efficacy) of immunosuppressant drugs over the immune cells of the patients, which are actually the target cells of the immunosuppressants/ immunomodulators. This "potency assay" would identify those immunosuppressants that may be more efficacious for each patient at a certain point of time.

Scientific approach to the problem

The immune system is very complex, dynamic and self-learning. Many different "immunological stories" may happen after birth, with infections, trauma, etc… leading to different immunological outcomes that vary day by day, although coming from similar genes. Because of this, it happens that genomics itself is not an approach capable of anticipating the full immunological risk profile of a patient at a certain point of time, nor the specific response to drugs.

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At Biohope we decided to design a “final point” immunoassay, in terms of a functional or pharmacodynamics assay. Under the different responses of immunosuppressants there are many factors (genetic, epigenetic, etc..) that combined can only be sufficiently addressed with functional bioassays which address the final “immune response profile” of the patient at a certain point of time. Treatment regimens must be changed along a patient’s life because the treatment efficiency varies over time as the immunological profile evolves over time in subsequent phases of the clinical condition (something similar like in the antibiotic resistance with infections that prolong in time).

Inmunobiogram®

BIOHOPE is developing a blood-based in vitro diagnosis test to give an important piece of information to personalize and monitor the adequacy of immunosuppressant therapy for each patient suffering from a chronic inflammatory condition who is under treatment with immunosuppressant drugs. This diagnostic kit been named Immunobiogram® (IMBG).

Biohope S.L. has developed a blood-based in vitro diagnosis test to support the health professionals in the management of transplanted kidney patients.

This tool will allow the physician to personalize the immunosuppressant therapy, selecting the most adequate medications and doses to avoid kidney rejection and reduce the side effects of treatment.

In the medium-term, Inmunobiogram® will be adapted and validated for a variety of disorders based on chronic inflammation as the major pathogenic cause, and are treated with immunosuppressive/immunomodulatory therapies, such as variants of progressive multiple sclerosis, Rheumatoid Arthritis, transplant rejection, among others.

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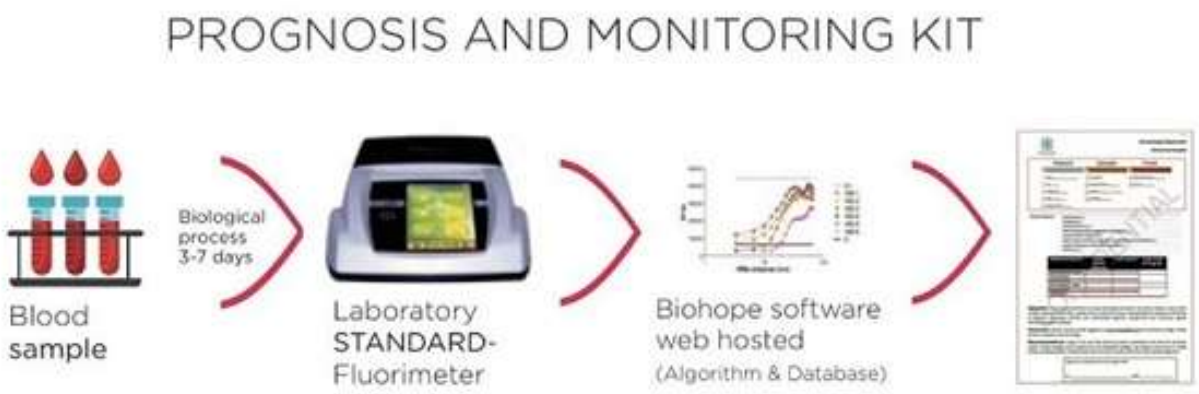
Only a conventional 10mL blood sample from the patient is needed to run the immunoassay. It is based on PBMCs 3D culture in semi-solid matrix submitted to specific stimulation which replicates antigen presentation. Inmunobiogram® mimics immune response in which PBMC replicate and expand (C+), and this response is compared with no stimulation (C-) and with stimulation in presence of immunosuppressants (C+ with IMs).



Data is analyzed with a software and output is an evaluation of the sensitivity degree of patient´s circulating immune cells to a panel of immunosuppressant most recommended in clinical guidelines and most used in the clinical setting. The bioassay uses well known immunosuppressants but it can be adapted for testing new compounds against marketed ones.

IMBG allows for a direct comparison between several immunosuppressant drugs in terms of immunosuppressive potency for each specific patient at the time the immunoassay is run.

As the immunological system is very dynamic and can be affected by many factors, it is anticipated that Inmunobiogram® would be better used as a test

to monitor patient´s intrinsic response to immunosuppressant drugs over time.

Several European patents were applied in 2017 to protect this invention.

Inmunobiogram® for RENAL TRANSPLANTATION

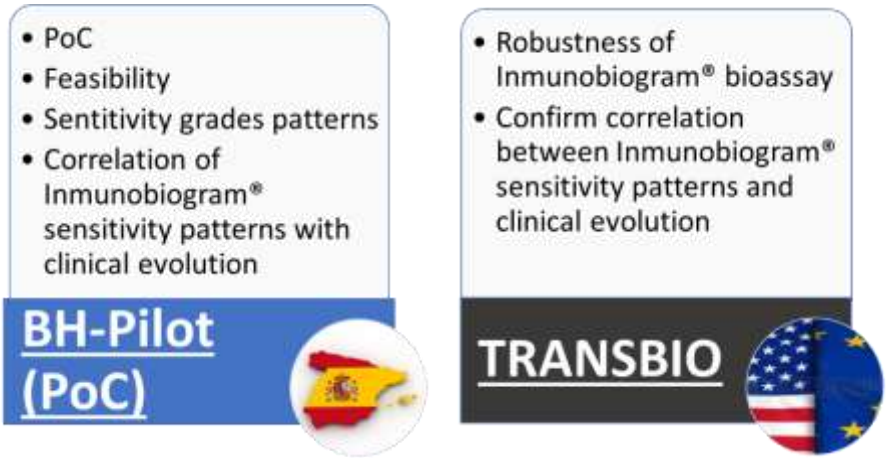
Inmunobiogram® is being studied in Renal Transplantation under a comprehensive clinical plan program, which includes a first proof of concept clinical study in 70 patients (BH-Pilot) and an international validation study in 200 patients (TRANSBIO clinical study)

"BH-Pilot" was a clinical study performed in 2017 in "La Paz" and "Puerta de Hierro" University Hospitals (Madrid). An interim analysis showing a positive proof of concept was presented at an investigator meeting with our Scientific Advisory Board held in the context of the European Society of Organ Transplantation (Barcelona, 24-27 September 2017). Final results coming from 70 patients indicate that Inmunobiogram® has shown the ability to measure the sensitivity of patients to Immunosuppressant medication (IMS), and on top of that, it can detect patients with bad prognosis due to IMS low sensitivity. The classification of immunoassay profiles, initially done by an expert, can be reproduced quite accurately by a neural network and thus completely automatized.

Final results from "BH-Pilot" will be first presented this year at the 27th International Congress of the Transplantation Society, TTS2018 (1-5 June, Madrid), http://tts2018.org/program/lunch-learn-sessions

TRANSBIO clinical study is an international (European and USA), multicenter, evaluation of the clinical consistency and analytical robustness of Immunobiogram® as an In Vitro Diagnostics BIOtechnological Tool to help decision-making in adjustment of immunosuppressant therapy for Renal TRANSplant (TRANSBIO study). This pivotal clinical study is beginning in May 2018 and it is expected to give conclusive results in 2019

R&D Pipelines



Current drugs tested in Inmunobiogram® - Transplant are:

CNI - inhibitors	Tacrolimus	Ciclosporin
Antiproliferative agents	Mycophenolic acid	Azathioprin
mTOR inhibitors	Sirolimus	Everolimus
Corticoids	Metilprednisolone	

Inmunobiogram® is an In Vitro Diagnostic laboratory test that combines a biotechnological KIT and a software for data interpretation. Inmunobiogram® bioassay is to be read with a luminometer or similar device. An automatic mathematical algorithm is been developed that, using rough data directly coming from the luminometer, offers a SCORE that evaluates patient´s individual sensitivity to the immunosuppressant panel of drugs. Due to its design and easy-to-read output, we anticipate it will be easily used in the clinical setting.

Several European patents were applied in 2017 to protect this invention.

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BH-Pilot Study

BH-Pilot study included 70 patients from "La Paz" and "Puerta de Hierro" University Hospitals (Madrid), classified into three categories depending on an immunological risk evaluation:

- High-risk patients (with a history of rejection, positive antibodies or impaired renal function, or combinations of previous criteria)
- Controlled patients (with conventional maintenance immunosuppression)
- Low-risk patients (without risk criteria and low levels of medication for years).

Data on patients' clinical and immunological history have been collected; an extensive battery of biomarkers has been performed on different platforms to complement the risk information, and 10Ml of blood has been taken to be tested at INMUNOBIOGRAM®.

Final results with the INMUNOBIOGRAM®, obtained in blood samples from 69 kidney transplanted patients and 7 healthy volunteers as a control group, clearly indicate a positive proof of concept.

The observed data can be summarized in the following points:

1) The INMUNOBIOGRAM® provides an **individualized patient response** pattern to immunosuppressive medication.

2) **Sensitivity ranges can be determined** in each patient for each of the drugs tested.

3) **Significantly associated low-sensitivity patterns have been observed in patients who present worse clinical evolution** and also receive higher doses of medication. These low-sensitivity patterns actually are more prominent to those drugs that patients are currently taking. **On the contrary, patients with a low-risk profile show better sensitivity scores** in Inmunobiogram® compared with standard patients and high-risk patients.

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In this clinical study, Inmunobiogram® has shown the ability to measure the sensitivity of patients to Immunosuppressant medication (IMS), and on top of that, it can detect patients with bad prognosis due to IMS low sensitivity.

A personalized information about which drugs show better sensitivity for each patient could be a useful information for the physicians to determine the best therapy regimen for their patients.

The classification of immunoassay profiles, initially done by an expert, can be reproduced quite accurately by a neural network and thus completely automatized.

TRANSBIO international multicenter clinical study

Title: ***Clinical consistency and analytical robustness of Immunobiogram® as an In Vitro Diagnostics BIOtechnological Tool to help decision-making in adjustment of immunosuppressant therapy for Renal TRANSplant. The TRANSBIO study***

TRANSBIO clinical study will include renal transplanted patients at least 1 year after the transplant (immunosuppression maintenance period).

ARM 1: this arm is intended to evaluate the correlation of Immunobiogram® sensitivity/resistance patterns with clinical prognosis as it may be judged at this moment considering clinical outcomes and immune-biomarker evolution in the past 12 to 18 months. Thus, it may confirm the BH-Pilot study findings. Renal transplant patients of two types will be included:

- Patients who, over previous months, have had a bad clinical evolution, in which rejection mechanisms were involved

- Patients with a good and stable clinical evolution

IMBG sensitivity/resistance profiles will be compared amongst the two groups to evaluate the differences.

ARM 2: this arm is intended to evaluate the robustness of Immunobiogram® as an IVD test. Thus, it will be performed intrasubject comparisons and inter-time evaluation of two sets of Immunobiogram® separated by 30+/- 10 days, each including three IMBG. Very stable Renal Transplanted patients will be included

The study is being done by an international multicenter validation study involving 200 patients in collaboration with a network of 7 renowned nephrologist of the following hospitals in Europe:

- Hospital Puerta de Hierro (Spain)
- Hospital Vall d´Hebron (Spain)
- Hospital del Mar (Spain)
- Hospital La Paz (Spain)
- Univesitätsklinikum Essen (Germany)
- Medical University Borowska (Poland)
- University Hospital of Copenhagen (Denmark)
- Massachusetts General Hospital, Harvard Medical School (Boston).

R&D Pipelines

Inmunobiogram® for RHEUMATOID ARTHRITIS

BIOHOPE is developing a blood-based in vitro diagnosis test to personalize immunosuppressant therapy for Rheumatoid Arthritis under treatment with immunosuppressant drugs. This diagnostic kit been named Immunobiogram® (IMBG) - Arthritis.

Inmunobiogram® is being studied in Rheumatoid Arthritis under a comprehensive clinical plan program, which includes a first proof of concept clinical study in 100 patients (BH-Pilot) and a subsequent validation study

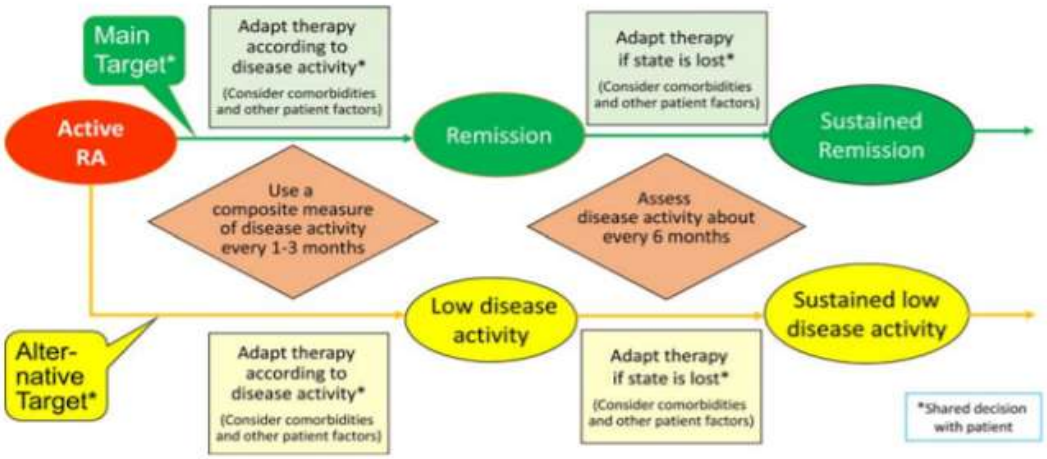
"BH-Arthritis" is a clinical study which aims to evaluate the feasibility and potential clinical utility of a specifically-developed Inmunobiogram® for Rheumatoid Arthritis. This first-in-clinic study is to be done in collaboration with the Rheumatology Unit of "Reina Sofía" Hospital (Córdoba) and "Maimonides Institute of Biomedical Research"

Worldwide, the annual incidence of RA is approximately three cases per 10,000 population, and the prevalence rate is approximately 1%, increasing with age and peaking between the ages of 35 and 50.

Clinical course of RA is very variable. More frequently, it follows a pattern of exacerbations and remissions. Outcomes are variable; some patients experience a relatively self-limited disease, whereas others have a chronic progressive illness. While there is no cure for RA, therapy for RA has improved greatly in the past 30 years. Today, patients begin their treatment with disease-modifying anti-rheumatic drugs, or DMARDs, which slow the progression of the disease. DMARDs have greatly improved the symptoms, function and quality of life for patients with RA.

The following chart, named 'treat-to-target', more precisely summarizes the preferred strategy for treatment of RA. The primary goals in the treatment of RA are to control inflammation and slow or stop disease progression. Currently, setting the goal, as well as initiating and adapting the therapy, should be done as a shared decision with the patient.

R&D Pipelines



Nevertheless, outcomes in RA are compromised when diagnosis and treatment are delayed. Despite treatments, approximately 40% of patients with this disease become disabled after ten years.

Unfortunately, DMARDs and also biological therapy are selected by trial and error. A personalized immunosuppressant approach cannot currently be implemented in clinical practice due to the lack of evidence-based tools towards selection of the optimal immunosuppressive therapy.

We are working to develop **BIOHOPE's IBMG-AR** as an In Vitro Diagnostic Tool that **will measure the sensitivity of patients to Immunosuppressant medication (IMS), and on top of that, detect patients with bad prognosis due to IMS low sensitivity. This information will allow to optimize treatment as soon as possible and guarantee a better outcome for the patient.**

Drugs aimed to be tested in Inmunobiogram® - Arthritis are:

Classic DMARDs	Methotrexate	Leflunomide	Sulfasalazine
	Hydroxychloroquine	Tacrolimus	Ciclosporin
Corticoids	Metilprednisolone		
New medicines	Tofacinib		

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Inmunobiogram®- AR is an In Vitro Diagnostic laboratory test that is expected to combine a biotechnological KIT and a software for data interpretation. Inmunobiogram® bioassay is to be read with a luminometer or similar device. An automatic mathematical algorithm will be developed that, using rough data directly coming from the luminometer, would offer a SCORE that evaluates patient´s individual sensitivity to the immunosuppressant panel of drugs. Due to its design and easy-to-read output, we anticipate it will be easily used in the clinical setting.

It is anticipated that further IP will be generated in this project.

BH- Arthritis Study

BH-Arthritis study is a clinical study to be conducted between 2018 and 1-2Q 2019 to evaluate the feasibility and potential clinical utility of a specifically-developed Inmunobiogram® for Rheumatoid Arthritis.

It will include 100 Rheumatoid Arthritis patients classified in the following categories:

1. Naïve patients (DAS>2)
2. Chronic patients under treatment with DMARDs with low disease activity
3. Chronic patients under treatment with DMARDs with high disease activity

We expect BH- Arthritis to be a clinical study that would demonstrate:

1) Inmunobiogram-AR (IMBG-AR) will be feasible in patients with Rheumatoid Arthritis at various disease stages and clinical scenarios
2) Inmunobiogram-AR (IMBG-AR) will offer as an output an in vitro potency evaluation of Immunosuppressant drugs (IMs) that will be correlated with sensitivity grades of the patient to a panel of IMs

3) A significant proportion of patients with non-controlled RA will show low-sensitivity patterns in IMBG-AR to the medication they are taking

This first-in-clinic study is to be done in collaboration with the Rheumatology Unit of “Reina Sofía” Hospital (Córdoba) and “Maimonides Institute of Biomedical Research”, and it is expected to start in 2Q2018.