LE STUDIUM
Loire Valley
Institute for Advanced Studies

LE STUDIUM Scientific Report
LE STUDIUM RESEARCH CONSORTIUM

INTRODUCTION

Each year, LE STUDIUM prepares an annual report that is tabled at the annual meeting of the Administrative Council and diffused widely. The 2017 annual report will present the scientific activities of LE STUDIUM projects. As your Consortium is funded by LE STUDIUM, to enable the preparation of an inclusive report, you are invited to submit a brief report according to the guidelines below. We recommend the report be prepared by the coordinator of the LE STUDIUM RESEARCH CONSORTIUM in collaboration with the partners of the project.

The questions and recommendations below are designed to help you present your project and field of research in the regional and international context. Your answer to these questions will help us to structure the document. Please note that the target audience of this scientific report includes non-specialists in your research field.

You are invited to send with your report, four or five pictures in high definition that could illustrate your project.

Should you have any questions do not hesitate to contact Aurélien Montagu (aurelien.montagu@lestudium-ias.fr).

Please use 12 point Arial Font for your report document

We thank you very much in advance.

1) MISSION OF THE HOST LABORATORY IN REGION CENTRE-VAL DE LOIRE

- What is the name of the laboratory partner of the project in region Centre-Val de Loire?
- What is its history?
- What is its mission?

(Total 12 to 15 lines)

GÉNÉTIQUE, IMMUNOTHÉRAPIE, CHIMIE ET CANCER (GICC) – UMR 7292 – UNIVERSITÉ FRANÇOIS-RABELAIS DE TOURS, CNRS

The GICC laboratory is focusing on the pathophysiological mechanisms of diseases, in order to set up and personalize therapeutics. Its current director is Gilles Thibault. The team PATCH (PhArmacology of TherapeutiC antibodies in Human; head Gilles Paintaud) aims at studying the mechanisms of action of monoclonal antibodies in the context of chronic diseases, by combining biology and mathematics. This quantitative systems pharmacology approach evolves a pathophysiologic system, in combination with a mathematical model, to understand the mechanism of action of monoclonal antibodies that are used in immune-inflammatory diseases and in cancer.

2) THE RESEARCH CONSORTIUM PROJECT

- What is the title of the consortium research project supported by LE STUDIUM?
- What are its ambitions?
- What are the achievements to date?

(Total 30-40 lines)

MONITORING OF MONOCLONAL ANTIBODIES GROUP IN EUROPE (MAGE) FOR INFLAMMATORY DISEASES

Biopharmaceuticals, in particular monoclonal antibodies, have radically transformed the course of various conditions, from malignancies to inflammatory diseases. Considerable inter-individual variability in the clinical response has been documented. It has been shown that pharmacokinetics (drug concentration versus time) is highly variable between patients and is related to clinical response, patients with high concentrations of the drug being more likely to respond than those who have low concentrations. Pharmacokinetic and pharmacokinetic- pharmacodynamic (PK-PD) modelling allows a description of the dose-response relationship to identify the sources of inter-individual variability, for both PK and PD-PD relationship. The team is seeking to explain this variability by studing the sources of the inter-individual variability that is observed in the response to monoclonal antibodies. Our work is based on both in vitro and preclinical models and on patient studies. Mathematical models are also used to quantify the influence of the individual sources of variability, to describe biological phenomena, and to design personalized dosage regimens for therapeutic antibodies. Over the last few years, academic groups have developed tools to monitor the pharmacological effect of therapeutic antibodies by means of measuring trough concentrations and biomarkers of disease activity. This practice called therapeutic drug monitoring (TDM), involves the measurement in sera of the concentration of the drug, often in combination with anti-drug antibodies (ADA) detection on the one hand, and the disease activity of patients on the other hand. TDM may help clinicians to adjust the dose regimen according to individual characteristics to improve clinical outcomes and avoid adverse events related to unnecessary overexposure. This strategy is relevant considering the economic burden of inflammatory chronic disease such as rheumatoid arthritis,Crohn's disease and multiple sclerosis. However, although TDM of biopharmaceuticals seems promising, its implementation in clinical settings deserves further research to develop reliable and standardized assays, mathematical modelling (population

approaches to analyze databases, mechanistic PK-PD modelling, clinical trial simulation) and clinical expertise.

The main aim of the MAGE consortium is to examine the scientific bases of the TDM of monoclonal antibodies in inflammatory diseases. This will be facilitated

1. to standardize assays for drug measurement,
2. to perform analyses in partnership to develop models for TDM
3. to design comparative effectiveness research to validate these tools.

3) COMMUNICATION RELATED TO THE PROJECT

- Make a list of communications related to your project for the 2016.
  - Oral communication (at regional, national and international level)
  - Poster (at regional, national and international congresses or seminaries)
  - Scientific publications

During the consortium activity the MAGE published eleven articles, as part of a focus issue on TDM of biopharmaceuticals in Therapeutic Drug Monitoring Journal (H Index=82) and one article in Clinical Pharmacology: Advances and Applications (H index=16).

1. Gils A, Bertolotto A, Mulleman D, Bejan-Angoulvant T, Declerck PJ. Biopharmaceuticals: Reference Products and Biosimilars to Treat Inflammatory Diseases. Ther Drug Monit. 2017 Aug;39(4):308-315.
2. Darrouzain F, Bian S, Desvignes C, Bris C, Watier H, Paintaud G, de Vries A. Immunoassays for Measuring Serum Concentrations of Monoclonal Antibodies and Anti-biopharmaceutical Antibodies in Patients. Ther Drug Monit. 2017 Aug;39(4):316-321.
3. Passot C, Pouw MF, Mulleman D, Bejan-Angoulvant T, Paintaud G, Dreesen E, Ternant D. Therapeutic Drug Monitoring of Biopharmaceuticals May Benefit From Pharmacokinetic and Pharmacokinetic-Pharmacodynamic Modeling. Ther Drug Monit.2017 Aug;39(4):322-326.
4. Bloem K, Hernández-Breijo B, Martínez-Feito A, Rispens T. Immunogenicity of Therapeutic Antibodies: Monitoring Antidrug Antibodies in a Clinical Context.Ther Drug Monit. 2017 Aug;39(4):327-332.
5. Paintaud G, Passot C, Ternant D, Bertolotto A, Bejan-Angoulvant T, Pascual-Salcedo D, Mulleman D. Rationale for Therapeutic Drug Monitoring of Biopharmaceuticals in Inflammatory Diseases. Ther Drug Monit. 2017 Aug;39(4):339-343.
6. Detrez I, Van Stappen T, Martín Arranz MD, Papamichael K, Gils A. Current Practice for Therapeutic Drug Monitoring of Biopharmaceuticals in Inflammatory Bowel Disease. Ther Drug Monit. 2017 Aug;39(4):344-349.
7. Caldano M, Raoul W, Rispens T, Bertolotto A. Drug Efficacy Monitoring in Pharmacotherapy of Multiple Sclerosis With Biological Agents. Ther Drug Monit. 2017 Aug;39(4):350-355.
8. Hermans C, Herranz P, Segaert S, Gils A. Current Practice of Therapeutic Drug Monitoring of Biopharmaceuticals in Psoriasis Patients. Ther Drug Monit. 2017 Aug;39(4):356-359.
9. Medina F, Plasencia C, Goupille P, Paintaud G, Balsa A, Mulleman D. Current Practice for Therapeutic Drug Monitoring of Biopharmaceuticals in Spondyloarthritis. Ther Drug Monit. 2017 Aug;39(4):360-363.
10. Medina F, Plasencia C, Goupille P, Ternant D, Balsa A, Mulleman D. Current Practice for Therapeutic Drug Monitoring of Biopharmaceuticals in Rheumatoid Arthritis. Ther Drug Monit. 2017 Aug;39(4):364-369.
11. Murias S, Magallares L, Albizuri F, Pascual-Salcedo D, Dreesen E, Mulleman D. Current Practices for Therapeutic Drug Monitoring of Biopharmaceuticals in Pediatrics. Ther Drug Monit. 2017 Aug;39(4):370-378.
12. Dreesen E, Bossuyt P, Mulleman D, Gils A, Pascual-Salcedo D. Practical recommendations for the use of therapeutic drug monitoring of biopharmaceuticals in inflammatory diseases. Clin Pharmacol. 2017 Oct 3;9:101-111.

4) PRESENTATION OF THE COORDINATOR OF THE PROJECT

- Briefly present your professional profile, achievements, awards etc?

(Total 10 lines)

Denis Mulleman is Professor of Rheumatology at the University François- Rabelais of Tours, member of the PATCH (PhArmacology of TherapeutiC antibodies in Human) team; head Gilles Paintaud. His research aims to characterise the concentration-response relationship of monoclonal antibodies used in inflammatory diseases, to help clinicians to individualise dosages, enabling personalised therapeutic drug monitoring. He is involved in numerous research projects using anti-TNF mAbs and Fc- containing fusion proteins, among them an Innovative Medicine Initiative (IMI) European project dedicated to the immunogenicity of biopharmaceuticals. His group has been deeply involved in the development of validated ELISA techniques allowing the quantification of serum concentrations of therapeutic antibodies. He is coordinator of designed clinical drug trials enabling population pharmacokinetic and pharmacokinetic-pharmacodynamic (PK-PD) modelling to quantify the different sources of the response interindividual variability.

5) COHERENCE OF THE CONSORTIUM

- Present each partner (title, name, organization, country, research field)?
- What does each partner bring to the consortium (which skills, which experience,…)?

(Total 15 lines)

The partners of the MAGE (Monitoring of Antibodies academic Group in Europe) have experience in clinical research on monoclonal antibodies and develop their research in academic laboratories. Given a strong expertise in pharmacology, immunology, and applied mathematics, the MAGE is gathering increasing scientific evidence to support a therapeutic drug monitoring of particular molecules in the field of inflammatory diseases. The MAGE consortium participants are at the crossover between

1. biology (assays, biomarkers),
2. clinic (patient cohorts and clinical trials),
3. mathematics (modelling).

Five institutions/laboratories constitute the MAGE whose representative are listed below:

Dr Antonio Bertolotto is Direttore dell'Unita Operativa di Neurologia 2 - Centro di Riferimento Regionale per la Sclerosi Multipla, Orbassano, Turin, Italy a large tertiary centre in charge of the clinical management of multiple sclerosis patients. The laboratory has an extensive experience in detection of binding antibodies in samples of patients treated with IFN beta and/or Natalizumab. This centre holds a large sample collection in a biobank as well as clinical and imaging data (MRI) of multiple sclerosis and related diseases.

Pr Ann Gils is a PI in the Department of Pharmaceutical and Pharmacological Sciences, KU Leuven Belgium, Laboratory for Therapeutic and Diagnostic Antibodies. The core business of the laboratory is the generation, characterisation and application of monoclonal antibodies. The laboratory has developed a number of assays to perform therapeutic drug monitoring and immunogenicity of biologicals, has an intensive collaboration with both the department of dermatology and of gastroenterology of University Hospital of Leuven and is involved in pharmacometrics.

Dr Dora Pascual-Salcedo is the head of autoimmune section in one of the biggest Hospitals in Spain, is an expert in autoimmunity at the University Hospital La Paz, Madrid. In her lab they perform test to identify and quantify autoantibodies in sera of patients with autoimmune diseases. She has excellent connections with rheumatologists (Dr Alejandro Balsa in particular), dermatologists and gastroenterologists. She has introduced in La Paz Hospital the systematic determination of drug

and anti-drug antibody levels for all patients at every visit, for most used biological drugs. She will contribute with her expertise in performance and interpretation of drug and anti-drug antibody levels, her knowledge of the clinical response associated with these parameters, her capacity to provide serum samples (more than 30.000 stored), her expertise in guiding Therapeutic Drug Monitoring in her Hospital, her collaboration with the pediatric rheumatology department.

Dr Gert Jan Wolbink is a rheumatologist and the PI of the Biologicals Research Unit at Jan van Breemen Research Institute/Reade, Amsterdam, The Netherdands, in the Rheumatology and Immunology Center investigating clinical strategies including therapeutic drug monitoring (TDM) for optimisation of treatment with biologicals. Together with Theo Rispens and Annick de Vries, he heads the Biologicals Research Group at Sanquin Immunopathology, which focusses on basic and translational research in the field of immunogenicity and TDM.