Pr DENIS MULLEMAN

CONSORTIUM COORDINATOR

LE STUDIUM CONSORTIUM | SMART LOIRE VALLEY

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.

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 personalised 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 standardised assays, mathematical modelling (population approaches to analyse 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.

PARTNERS

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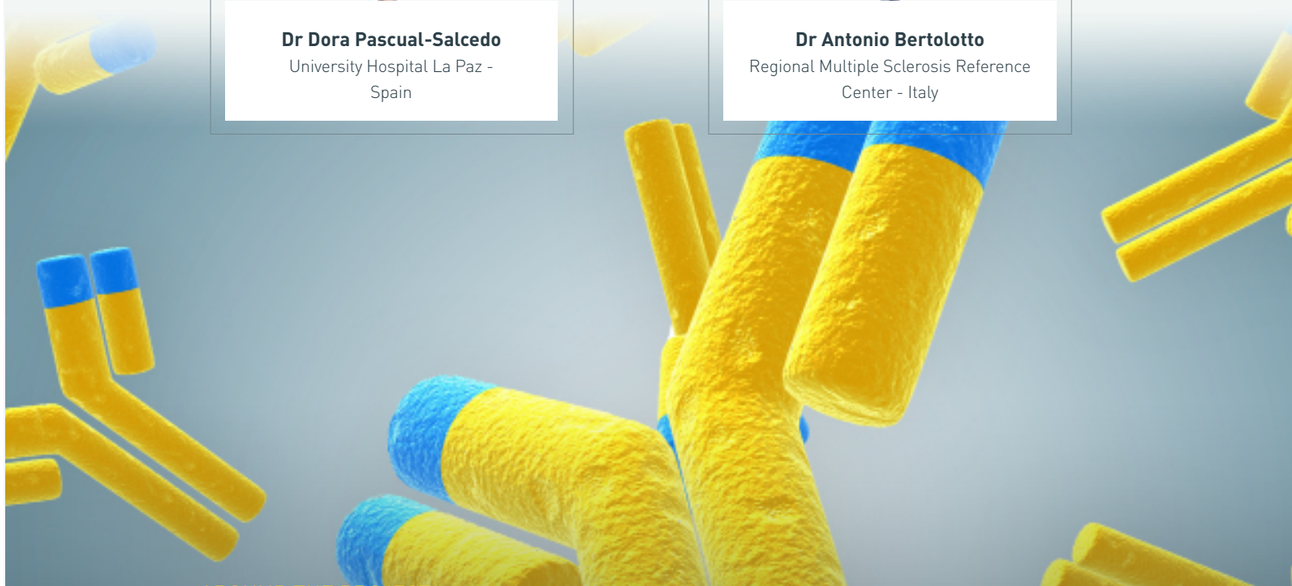

AROUND THE PROJECT

Scientific Publications

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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**, *9*, 101-111.