PSI One Day Meeting: Immunology Diseases

Friday 17th June - Roche Products Limited, 6 Falcon Way, Shire Park, Welwyn Garden City, Al7 1TW

Immunology is a branch of biomedical science that covers the study of all aspects of the immune system; this may include autoimmune diseases, such as Rheumatoid Arthritis; transplant rejection; infections. During this one day meeting, PSI aims to cover a wide range of immunology diseases, design considerations and statistical challenges when working in this therapeutic area. We hope that sharing between different areas on Immunology; will stimulate interesting discussion and an opportunity to knowledge share.

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| 9.30 -9.55 | Registration |
| 9.55 – 10.00 | Welcome and Introduction |
| 10.00 – 10.30 | Clinical Overview of Immunology Diseases |
|  | Chris Mela : Roche |
| 10.30 – 11.15 | An approach for integrating existing knowledge into the statistical analysis  of multiple immune markers:  An application to cytokine data collected in a large immuno-epidemiological study aimed to investigate risk factors for atopy and asthma |
|  | Dr Bernd Genser1,2 & Marion Genser1  1 BGStats Consulting Vienna Austria  2 Mannheim Institute of Public Health, Social and Preventive Medicine, University of Heidelberg, Germany |
| 11.15 – 12.00 | Innovative dose escalation and dose finding in immunology |
|  | Alun Bedding: AstraZeneca |
| 12.00 – 12.45 | Lunch |
| *12.45 – 1.25* | Leveraging Data across Multiple Immuno-Inflammation Indications: Early Clinical Development of a Novel Compound |
|  | Nicola Scott : GSK |
| 1.25 – 2.05 | Complex study design in patients with Hereditary Periodic Fevers, an orphan autoimmune disease |
|  | Karine Lheritier : Novartis |
| 2.05 – 2.45 | Engineering Simulations to Understand and Gain Inspiration From Biological Systems |
|  | Kieran Alden : York Computational Immunology Lab |
| 2.45 – 3.05 | Coffee |
| 3.05 – 3.45 | A bioequivalence study design which includes the option for sample size re-estimation (SSR) at the Interim Analysis |
|  | Jen Pulley: Roche |
| 3.45 – 4.25 | RA-MAP Project - Towards an  improved understanding of immune function and response in RA |
|  | Brian D M Tom (PhD)  Programme Leader  MRC Biostatistics Unit |
| 4.25 – 4.30 | Close |

**Clinical Overview of Immunology Diseases**

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| **Chris Mela**  Roche Products Ltd | Immunology is viewed as a complex and daunting subject with a multitude of antibodies, interleukins, molecules, cells and pathways that interact in mysterious ways. This perception can worry anyone stating research in a new immunological area or disease. The reality is that the immune system spans almost every disease from aging to zoonosis and that certain concepts are common across all of these. By understanding some of these themes we can demystify immunology and turn the fear into fascination. |

**An approach for integrating existing knowledge into the statistical analysis of multiple immune markers: An application to cytokine data collected in a large immuno-epidemiological study aimed to investigate risk factors for atopy and asthma**

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| **Dr Bernd Genser1,2**  *1. BGStats Consulting Vienna Austria*  *2. Mannheim Institute of Public Health, Social and Preventive Medicine, University of Heidelberg, Germany* | BACKGROUND: Immunologists often measure several correlated immunological markers, such as concentrations of different cytokines produced by different immune cells and/or measured under different conditions, to draw insights from complex immunological mechanisms. Although there have been recent methodological efforts to improve the statistical analysis of immunological data, a framework is still needed for the simultaneous analysis of multiple, often correlated, immune markers. This framework would allow the immunologists’ hypotheses about the underlying biological mechanisms to be integrated.  METHODS: We present an analytical approach for statistical analysis of correlated immune markers, such as those commonly collected in modern immuno-epidemiological studies.  RESULTS: We demonstrate i) how to deal with interdependencies among multiple  measurements of the same immune marker, ii) how to analyse association patterns among different markers, iii) how to aggregate different measures and/or markers to immunological summary scores, iv) how to model the inter-relationships among these scores, and v) how to use these scores in epidemiological association analyses. We illustrate the application of our approach to multiple cytokine measurements from 818 children enrolled in a large immuno-epidemiological study (SCAALA Salvador), which aimed to quantify the major immunological mechanisms underlying atopic diseases or asthma. We demonstrate how to aggregate systematically the information captured in multiple cytokine measurements to immunological summary scores aimed at reflecting the presumed underlying immunological mechanisms (Th1/Th2 balance and immune regulatory network). We show how these aggregated immune scores can be used as predictors in regression models with outcomes of immunological studies (e.g. specific IgE) and compare the results to those obtained by a traditional multivariate regression approach.  CONCLUSION: The proposed analytical approach may be especially useful to quantify complex immune responses in immuno-epidemiological studies, where investigators examine the relationship among epidemiological patterns, immune response, and disease outcomes. |

**Innovative dose escalation and dose finding in immunology**

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| **Alun Bedding**  AstraZeneca | Many drugs that are being developed for auto-immune diseases, such as type I diabetes or ulcerative colitis have the potential to impact regulatory T-cells.  However, they also may impact the t-effector cells which may cause serious side effects.  New, innovative study designs are needed to be developed in order to study the dose response of these compounds.  Recent work by Waldron-Lynch et al (2014) has given rise to the potential of using exploratory adaptive dose finding designs in order to better characterise the dose response curves.  This talk will give details of potential dose escalation and dose finding designs that build on the work of Waldron-Lynch et al.  Innovative Bayesian, adaptive designs will be introduced with simulations of studies to show the operating characteristics. |

**Leveraging Data across Multiple Immuno-Inflammation Indications: Early Clinical Development of a Novel Compound**

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| **Nicola Scott**  GSK | Recent research has identified that necroptosis is the major driver of TNF-α dependent inflammation and disease. A clinical development program for a first in class compound is currently assessing a target which blocks solely the TNF-α necroptosis pathway. Following completion of the First Time in Human study, we will next focus in on the human validation of blocking this pathway, which in turn will result in a greater understanding of the compound and mechanism early in clinical development.  This will be achieved through experimental medicine (EM) studies in three Immuno‑Inflammation indications that are treated with anti-TNFs: Psoriasis, Rheumatoid Arthritis and Ulcerative Colitis.  Each study is extremely data rich due to the number of biomarkers, mechanistic and efficacy endpoints that will be collected.  These EM studies will be conducted in parallel, thus providing a unique opportunity to leverage data across the three indications in order to benchmark against anti-TNFs, and thus inform the clinical development of this compound |

**Complex study design in patients with Hereditary Periodic Fevers (HPF), an orphan autoimmune disease.**

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| **Karine Lheritier PhD** Novartis | Familial Mediterranean fever (FMF), Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS) and TNF-receptor–associated periodic syndrome (TRAPS) are a cluster of autoimmune disease called HPF syndromes. These are rare and distinct heritable disorders characterized by short and recurrent attacks of fever and severe localized inflammation that occur periodically or irregularly.  The planning of a single study within this cluster of autoimmune disease presents multiple and complex design challenges. Canakinumab is an anti-interleukin-1β monoclonal antibody being developed for the treatment of IL-1β - driven inflammatory diseases and has already been shown to be effective in patients with CAPS which is also classified under this single term of HPF syndromes.  Efficacy and safety of Canakinumab in colchicine resistant FMF, HIDS and TRAPS patients have been shown in phase II studies. However, there are currently no approved treatments for  these conditions. Our challenge was to design a single study on patients suffering from these 3 rare conditions. This required inclusion of a randomised, double-blind, placebo-control and a randomized withdrawal element, a long-term follow-up part, in addition to clinical constraints such as up-titration of the dose, change in the dose frequency, co-primary efficacy endpoints with different timepoints. Requests from different health authorities such as the Paediatric Committee at the European to include patients >28 days in this clinical trial were also built into the design. |

**A bioequivalence study design which includes the option for sample size re-estimation (SSR) at the Interim Analysis**

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| **Jen Pulley**  Roche | In Immunology we are currently designing a bio-equivalence study using a two stage sample size re-estimation adaptive design. This design will allow the sample size assumptions to be re-evaluated once approximately half the subjects have completed the study.  Our initial study design used overall power and fixed analysis with no adjustment for type I error. This design was rejected by the health authorities so the team revised the study design. Two revised study designs using conditional power with a promising zone was proposed to health authorities. Each of the two revised designs made the adjustment for the type I error within the 90% CI calculation using either the t-distribution method or adjusted normal method.  This presentation will discuss the methods used for the revised SSR study designs and the ongoing interactions with health authorities. |

**RA-MAP Project - Towards an improved understanding of immune function and response in RA**

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| **Brian Tom**  MRC Biostatistics Unit | There is compelling evidence to implicate dysregulated immune function in the pathogenesis (origin and progression) of rheumatoid arthritis (RA). The RA-MAP Project is an MRC/ABPI Inflammation and Immunology Initiative that aims to improve understanding of the human immune system in rheumatoid arthritis, using ex vivo and functional read outs, through the application of established and new technologies and through different complementary studies. We conjecture that discrete, dynamic immunological profiles are present in leucocyte subsets, plasma or serum derived from human blood that are informative of current and future disease states in RA (or health) and thereby relevant immune function.  In this talk, I will describe the plan of investigation adopted, the data collected and the statistical methodology that may be used to investigate immune dysregulation in RA by the RA-MAP consortium. |