Abstracts

IBD

**OTU-001 IDENTIFICATION OF A NOVEL THERAPEUTIC AGENT FOR TREATING IBD GUIDED BY SYSTEMS MEDICINE**

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**Introduction** There remains an unmet need in the treatment of IBD. The SysmedIBD project established a multi-disciplinary consortium to systematically investigate patients with inflammatory bowel disease, focusing on the dynamics of NF-kB signalling. Through this approach we identified an established drug with potential for repurposing to treat IBD, in selected patients.

**Methods** Novel targets with potential for impacting outcomes of IBD were identified in-silico by combining integrated promoter/pathway analysis of published microarray data and systematic text-mining of the published literature using the geneXplain software platform. An established drug with potential for repurposing was assessed as a proof-of-concept agent using a multi-step validation pipeline based on its effect on NF-kB dynamics in-vitro and in-vivo, and its ability to ameliorate murine experimental colitis.

**Results** 3191 pharmacological agents (Prestwick Chemical Library) were assessed in-silico. 36 agents were highly significantly predicted to influence NF-kB and other IBD target activity. Amongst the highest ranked agents were the macrophage antibiotics. Clarithromycin (CLA) was selected as a paradigm for subsequent analyses.

The effects of CLA were investigated in 5 experiments:

1. NF-kB mediated transcription was investigated using peritoneal macrophages and enteric organoids from a mouse expressing firefly luciferase under the control of the human TNF promoter: CLA suppressed responses in both tissues (p<0.05).
2. NF-kB(p65) protein shuttling dynamics were characterised in enteric organoids cultured from a mouse expressing human p65–dsRed: CLA suppressed TNF induced oscillation of p65 (p=0.0002).
3. C57BL/6 mice were treated with intra-peritoneal LPS (0.125 mg/kg) to induce small intestinal NF-kB activation: CLA suppressed DNA binding of p65 (p=0.002).
4. The effect of CLA on DSS colitis was studied: mice treated with CLA lost significantly less weight (p<0.05), and had less severe histology than mice treated with vehicle (p=0.004).
5. The effect of CLA on TNF induced nuclear localisation of p65 in human enteric organoids was studied: CLA suppressed p65 nuclear localisation (p<0.0001).

**Conclusions** Using a systems biology approach, we have identified an agent with potential for repurposing to treat IBD. Outcomes of earlier clinical trials of clarithromycin were discordant: we are developing a biomarker of NF-kB responsiveness that may enable precise selection of patients for a personalised medicine trial.

**OTU-002 HLA-DQA1 CONTRIBUTES TO THE DEVELOPMENT OF ANTIBODIES TO ANTI-TNF THERAPY IN CROHN’S DISEASE**

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**Background** Immunogenicity to anti-TNF therapy is a major cause of loss of response, treatment discontinuation and hypersensitivity reactions and currently cannot be predicted prior to treatment. A number of factors have been associated with the risk of immunogenicity, but knowledge of the cellular and molecular mechanisms remain limited. Our aim was to investigate genetic susceptibility to immunogenicity.

**Methods** The PANTS (Personalised Anti-TNF Therapy in Crohn’s disease) study is a 3 year prospective observational UK-wide study investigating primary non-response, loss of response and adverse drug reactions to the anti-TNF drugs infliximab and adalimumab. Anti-drug antibodies (ADAs) were measured serially at trough using the IDKmonitor total ADAs ELISA assay. Immunogenicity was defined as (a) ADA titre ≥10 AU/ml and (b) ADA titre ≥10 AU/ml with no detectable drug. A genome-wide association study (GWAS) was carried out on imputed genotypy data using a Cox proportional hazards model incorporating the anti-TNF used and presence of concomitant immunomodulator as covariates (SurvivalGWAS SV v1.3.1).

**Results** After quality control, we had genotypy data for 1284 patients followed prospectively for a minimum of 12 months since starting anti-TNF therapy. Using a Cox proportional hazards model and an immunogenicity definition of ADAs titre ≥10 AU/ml we identified a genome-wide association on chromosome 6 (top SNP rs74291249 with p=5.6 × 10−13). We imputed the HLA alleles at 2- and 4-digit resolution using the HIBAG package and demonstrated that this signal was driven by HLA-DQA1*05 for both infliximab and adalimumab. No additive effect of having two DQA1*05 was seen. Figures 1 and 2 show immunogenicity-free survival stratified by HLA-DQA1*05 genotypy and concomitant immunomodulators at baseline.

Abstract OTU-002 Figure 1 Immunogenicity by immunomodulator and HLA-DQA1*05 for infliximab and adalimumab.