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-κB 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-κB 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-κB and other IBD target activity. Amongst the highest ranked agents were the macro-lide antibiotics. Clarithromycin (CLA) was selected as a paradigm for subsequent analyses.

The effects of CLA were investigated in 5 experiments:

1. NF-κB 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-κB(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-κB 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-κB 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 ADAb 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 genotype 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 genotype 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 $p = 5.6 \times 10^{-13}$). 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 genotype and concomitant immunomodulators at baseline.

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