Using systems medicine to identify a therapeutic agent with potential for repurposing in Inflammatory Bowel Disease

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Abstract:

Objective: Inflammatory bowel diseases cause significant morbidity and mortality. Aberrant NF-κB signalling is strongly associated with these conditions, and several established drugs influence the NF-κB signalling network to exert their effect. This study aimed to identify drugs which alter NF-κB signalling and may be repositioned for use in inflammatory bowel disease.

Design: The SysmedIBD consortium established a novel drug-repurposing pipeline based on a combination of in-silico drug discovery and biological assays targeted at demonstrating an impact on NF-kappaB signalling, and a murine model of IBD.

Results: The drug discovery algorithm identified several drugs already established in IBD, including corticosteroids. The highest-ranked drug was the macrolide antibiotic Clarithromycin, which has previously been reported to have anti-inflammatory effects in aseptic conditions.

Clarithromycin's effects were validated in several experiments: it influenced NF-κB mediated transcription in murine peritoneal macrophages and intestinal enteroids; it suppressed NF-κB protein shuttling in murine reporter enteroids; it suppressed NF-κB (p65) DNA binding in the small intestine of mice exposed to LPS, and it reduced the severity of dextran sulphate sodium-induced colitis in C57BL/6 mice. Clarithromycin also suppressed NF-κB (p65) nuclear translocation in human intestinal enteroids.

Conclusions: These findings demonstrate that *in-silico* drug repositioning algorithms can viably be allied to laboratory validation assays in the context of inflammatory bowel disease; and that further clinical assessment of clarithromycin in the management of inflammatory bowel disease is required.

Keywords:

Inflammatory Bowel Diseases

NF-kappa B

Drug Repositioning

Interdisciplinary research

Organoids

Macrolide

Ulcerative colitis

Crohn’s disease

Introduction:

Inflammatory bowel diseases (IBD) affect 0.5-1.0% of people in the Western world and cause substantial morbidity and cost to society(Feagan et al., 2014; van Deen et al., 2014). The aetiology of IBD is complex. There are aberrant inflammatory responses, leading to mucosal damage and the disease phenotype.

Diverse therapeutic approaches are employed: Many patients with mild ulcerative colitis are treated with mesalazine preparations, which predominantly act topically on the colonic mucosa to suppress inflammation(Marteau et al., 2005), others require systemic therapy with highly-specific biologic agents targeting inflammatory mediators(Baert et al., 1999; Targan et al., 1997). While these drugs have very different mechanisms of action, they influence host inflammatory responses and either directly or indirectly alter NF-κB signalling.

The NF-κB signalling network is a tightly-controlled, dynamically-regulated signal transduction pathway with several well-described transcription regulatory feedback loops(Lev Bar-Or et al., 2000): this orchestrates innate immune responses by regulating transcription through dimers of the five NF-κB proteins (RelA(p65), RelB, NF-κB1(p50), NF-κB2(p52) and c-Rel). Signalling through this network is characterised by the oscillation of NF-κB proteins between the cytoplasm and nucleus; most clearly demonstrated for the RelA(p65) subunit(Nelson et al., 2004). In addition to changes in the inflammatory milieu, this network also affects several other processes which are dysregulated during chronic gastrointestinal inflammation including cell turnover, DNA damage responses and cell senescence(Perkins, 2012). Several studies have associated aberrant NF-κB signalling with IBD (reviewed in refs(Atreya et al., 2008; McDaniel et al., 2016; Merga et al., 2016)).

Because of the complexity of NF-κB signalling, targeting specific components of the network has not been a successful drug development strategy to date, mainly because of the ubiquitous nature of NF-κB signalling. The impact of gross inhibition of critical members of

the NF-κB signalling cascade has been unpredictable and associated with undesirable off-target effects. The complexity of NF-κB signalling during GI tract inflammation is elegantly demonstrated by murine work. When transgenic mice lacking specific NF-κB sub-units were subjected to a DSS model, mice lacking *cRel* and *Nfkb1* developed more severe colitis than wild-type controls, whilst *Nfkb2-/-* mice were resistant to colitis(Burkitt et al., 2015). C57BL/6 mice lacking IKKbeta in epithelial cells were more severely affected by DSS colitis(Greten et al., 2004), whilst IL-10-/- mice lacking IKKbeta in the intestinal epithelium had similar colitis to those with intact NF-κB signalling but in both these models loss of IKKbeta in myeloid cells attenuated colitis and improved survival(Eckmann et al., 2008). It is therefore likely that the transcriptomic effects of attenuating NF-κB signalling in the epithelium and myeloid compartments is different,

This complexity has promptied calls for highly specific inhibitors which target components of the network in precisely-selected cell types(Baud and Karin, 2009). This approach is useful in certain circumstances such as multiple myeloma, where targeting a specific cancer cell lineage is desirable and may be achievable. In contrast, for complex benign inflammatory diseases, including IBD, this strategy is less likely to be successful due to challenges in identifying a specific target cell population.

We propose an alternative strategy, to 'nudge' an individual's NF-κB signalling network towards an idealised healthy phenotype. This approach may offer a more pragmatic way of targeting aberrant NF-κB signalling, without the limitations of selective tissue targeting or gross pathway inhibition.

To investigate this in the context of inflammatory bowel disease, we used a combination of novel bioinformatic analyses and laboratory studies to identify agents likely to impact NF-κB signalling and inflammatory bowel disease. Because of the divergent roles of myeloid and epithelial NF-κB signalling during GI tract inflammation, we have established assays to

measure the effects of drugs on both epithelial and immune tissues. We then validated the efficacy of the most highly ranked agent, both in terms of inhibiting NF-κB activity, and modulating an *in-vivo* model of colitis.

Methods:

Pathway analysis for master regulator search

Molecules that regulate the expression of differentially expressed genes through control of the activity of NF-κB sub-units were defined as master regulators and were identified by applying a key-node analysis algorithm(Kel et al., 2006) using the TRANSPATH® database of gene regulatory and signal transduction pathways(Krull et al., 2006).

Key-nodes were prioritised based on the weighted ratio between the number of molecules from the input set that could be reached from the key-node in ≤10 steps and the total number of reachable nodes. The higher the score, the greater the chance that the key-node plays a master regulatory role.

In-silico drug discovery

Relationships between the chemical structure of compounds and their biological activities were analysed using large-scale prediction of activity spectra(Filimonov et al., 1995; Poroikov et al., 2001) (http://genexplain.com/pass/) to discover potential new drugs for IBD treatment. The PASS algorithm is based on Bayesian estimates of probabilities of molecules belonging to the classes of active and inactive compounds(Filimonov et al., 2014). The predicted activity spectrum is presented in PASS by the list of activities with probabilities "to be active" Pa and "to be inactive" Pi calculated for each activity.

For each compound of the tested library, a cumulative score was computed across the 46 PASS activities selected in the previous analysis.

$$Score = \sum_{i=1}^{46} p_a(i)$$

here $p_a(i)$ is the probability for the given compound to be active for each activity *i*.

For each compound tested, the cumulative score was required to be higher than 3.0, and the Pa for the PASS activity "Transcription factor NF-κB inhibitor" was positive.

Patient recruitment and ethics

Samples used for the generation of human enteroids were donated by patients without evidence of IBD attending for colonoscopy at the Royal Liverpool and Broadgreen University Hospitals NHS Trust. Samples were collected following written informed consent and favourable ethical opinion from North West-Liverpool East Research Ethics Committee (15/NW/0045).

Animal maintenance and welfare

All animal breeding, maintenance and procedures were performed under a UK Home Office licence, with local Animal Welfare and Ethics Review Board approval. Transgenic animals were maintained at the University of Manchester. Wild-type mice were purchased from Charles River (Margate, UK) and maintained either at the University of Manchester or University of Liverpool in SPF facilities with access to standard chow and drinking water *ad-libitum* unless otherwise specified. Standard 12-hour light/dark cycles were used; standard temperature and humidity levels were maintained.

Transgenic mouse strains

Human TNFα luciferase mice (hTNF.LucBAC)

This line has been engineered to have a bacterial artificial chromosome (BAC) expressing luciferase under the regulation of the entire human TNF promoter. Primary cultures established from this mouse enable direct measurement of TNF promoter activity in a non-transformed *ex-vivo* system(Minshawi et al., 2019).

Human p65-DsRedxp/IκBalpha-eGFP mouse (p65-DsRedxp/IκBalpha-eGFP).

This line expresses fusion proteins of NF-κB(p65) and the *Discosoma* red fluorescent protein – Express (DsRedxp) under the regulation of the native human p65 promoter, and IκBalpha and enhanced green fluorescent protein (eGFP), regulated by the human IκBalpha promoter(Dudek et al., 2017). Primary cultures established from this mouse enable direct visualisation of these fusion proteins.

Peritoneal macrophage isolation, in vitro culture and luciferase assay

Resident peritoneal macrophages were obtained from mice by standard methods. Cells were stimulated with either 10ng/mL LPS (*Salmonella enterica* serovar Minnesota R595; Calbiochem), TNF (R&D Systems) at 40 ng/mL, muramyl dipeptide (MDP, Invivogen) at 10µg/mL or Flagellin (Novus Bio) at 500ng/ml. Luciferase activity was measured over time in a CO_2 luminometer (Lumistar Omega, BMG Labtech).

Flow Cytometry

Peritoneal macrophages were stimulated with 1µg/ml LPS for 20min. Fixed cells were stained for phosphor-p65 (PE Mouse anti-NF-κB p65 (pS529), BD Bioscience, clone K10-895.12.50) and analysed by flow cytometry using an LSRII Cytometer (BD). Data analyses were performed with FlowJo887 software (Tree Star).

Primary Epithelial cell culture

Enteroids were generated from human and murine tissue using modifications of established protocols. Tissue samples were disaggregated by calcium chelation in EDTA followed by mechanical disaggregation in a sucrose/sorbitol solution. Crypt pellets were resuspended in Matrigel (Corning, UK) and were maintained in media containing a combination of recombinant growth factors and growth factor containing conditioned media (supplemental methods). Enteroids were passaged at least once prior to experiments.

Enteroid immunohistochemistry

Enteroids were pre-treated with 10µM clarithromycin or 1% v/v DMSO (vehicle) for 30mins. Following pre-treatment, 100ng/mL recombinant human TNF (Peprotech) was applied for a further 30mins. Fixed enteroids were transferred into Richard-Allan™ Histogel™ (Thermofisher) and processed for histology. Immunohistochemical analysis was performed to visualise p65 (Cell Signaling Technologies, #8242). The proportion of cells nuclear stained for p65 was quantified using manual cell counting. First, for one tissue section of an organoid all nuclei were counted using a handheld tally counter. Immediately afterwards, the same section was scored for number of positively stained nuclei and the percentage calculated. The individual scorer was experienced in quantitative histology techniques (KL) and blinded to the experimental conditions for each sample.Murine intestinal organoid confocal microscopy

Proximal enteroids from p65-DsRedxp/IκBalpha-eGFP dual-reporter mice were passaged into glass-bottom dishes (Thermo Scientific™ Nunc™ Glass Bottom Dishes) in phenol red-free complete media. Images were taken for 6-8 enteroids per dish using a Zeiss Laser Scanning Microscope (LSM880) with a C-Apochromat 40x/1.2 W Korr FCS M27 objective. Enteroids were imaged for 30mins before treatment with 10µM clarithromycin or 1% v/v DMSO vehicle. Thirty minutes later, cultures were stimulated with 100ng/ml TNF and imaged for a further 3hrs. Images and videos were processed using Zen 2011 software and CellTracker (Warwick Systems Biology Centre).

LPS-induced NF-κB activation in mice

Groups of adult (8-10-week-old) male C57BL/6 mice received 50mg/kg clarithromycin i.p, or vehicle daily for three days. Following a 3-day washout period, either 50mg/kg clarithromycin i.p., or 0.9% w/v saline vehicle was administered, the next day either 50mg/kg clarithromycin i.p. or vehicle was followed by either 0.125mg/kg ultrapure LPS from *E. coli* K12 (Invivogen) i.p. or 0.9% w/v saline vehicle. Animals were culled 90 minutes after LPS/vehicle

administration; small intestinal mucosal scrapes were prepared in RIPA buffer with protease inhibitors (Sigma, Gillingham, UK). NF-κB p65 DNA binding was quantified using a TransAM DNA-binding ELISA (ActiveMotif, La Hulpe, Belgium).

Dextran sulphate sodium-induced colitis

Groups of adult (8-10-week-old) male C57BL/6 mice were administered either 10 mg/kg clarithromycin, or vehicle by orogastric gavage daily for four days. Following a washout period, animals received 2.5% DSS in drinking water, for five days. Animals recovered for a further three days. From the start of DSS treatment to termination of the experiment either 10 mg/kg clarithromycin or normal saline vehicle was administered by daily orogastric gavage. Tissue samples were harvested and prepared for histological analysis, including quantitative histology, as previously described(Williams et al., 2016).

Statistical analysis of laboratory work

Statistical analyses were performed using GraphPad Prism v.7.0 software. Specific statistical tests are annotated in the text and figure legends. Reported *p*-values are two-tailed. Normality testing was performed with the D'Agostino & Pearson test.

Results:

To predict drugs that may influence disrupted NF-κB signalling in IBD, a drug-discovery strategy combining data from multiple sources (archived ChIP-seq analyses; natural language text-mining of published abstracts; data from IBD GWAS analyses; and known IBD biomarkers and drug targets curated in the HumanPSD database) was developed (Figure 1).

Developing an enhanced NF-κB signalling network

Signalling molecules comprising (transcription) regulatory feedback loops present promising drug targets because they can influence the dynamics of a signalling pathway of interest, including the TNF-alpha/NF-κB pathway. To augment existing knowledge about NF-κB signalling, we developed an analysis workflow to identify genes encoding potential

components of transcription regulatory feedback loops combining known NF-κB-involving signalling pathways, ChIP-seq assay based NF-κB/RelA-bound genomic regions from the ENCODE project (GEO series GSE31477), and a newly-developed method to find combinations of enriched DNA-sequence motifs (Motif Enrichment Analysis by Logistic Regression (MEALR)) (see supplementary materials for details). Combinations of prioritised motifs tend to coincide with transcription factors that are known to cooperate. Our analysis found 24 transcription factors that appear to cooperate in NF-κB signalling within the genomic regions reported by ENCODE (Table 1) as well as 90 potential NF-κB/RelA-target genes that encode components of known pathways. (Table 2). The results were used to annotate the TRANSPATH® database of mammalian signal transduction and metabolic pathways.

Text mining to establish context proteins and genes for up-stream network analyses

1000 relevant abstracts were retrieved using the MedlineRanker tool(Gijon-Correas et al., 2014) from the PubMed database using the MeSH terms “Inflammatory bowel diseases” and “NF-κB”. Protein-protein interactions were identified in these abstracts using PESCADOR(Barbosa-Silva et al., 2011). PESCADOR detects genes, proteins and their interactions, and rates them based on co-occurrences in an abstract. 827 interactions common for both *Homo sapien*s and *Mus musculus*, 2 for *Mus musculus* alone, and 26 uniquely for *Homo sapiens* were extracted (Supplementary Table S1). After querying the TRANSPATH® database for known direct interactions, 127 novel co-occurrences of genes or proteins in the abstracts analysed. This table of interactions was used to provide context to subsequent up-stream network analysis to impute the key regulatory nodes for NF-κB signalling in IBD.

Identifying master regulators of the NF-κB signalling network

An upstream search of the various molecular components of NF-κB complex including: NF-κB1-isoform1, NF-κB1-isoform2, NF-κB2-isoform4, NF-κB2-p100, NF-κB2-p49, RelA-p35, RelA-p65-delta, RelA-p65-delta2, RelA-p65-isoform1, RelA-p65-isoform4, RelB, c-Rel was performed. The network search extended to a maximal radius of 10 steps upstream of the NF-κB components and used a false discovery rate (FDR) cut-off of 0.05 and Z-score (reflecting how specific each master regulator was) cut-off of 1.0. The list of interacting proteins obtained by text-mining was used to provide "Context proteins" for the master-regulator acquisition algorithm(Kel et al., 2016). This analysis revealed 325 controlling nodes predicted to exert signalling activity for the NF-κB components (Table S2).

Developing a list of IBD associated genes and potential therapeutic targets

A list of IBD associated-genes and potential therapeutic targets was established by retrieving information from the HumanPSD database including known IBD biomarkers and drug targets, and two lists of IBD-related genes from genome-wide association studies, one focused on revealing genes of IBD prognosis(Lee et al., 2017), and another on IBD susceptibility(Hasler et al., 2017). 159 IBD-targets were identified and summarised with an indication of the source of evidence about their relevance to IBD (Table S3).

Finally, to produce a list of proposed therapeutic targets the list of IBD-targets was intersected with the 325 controlling nodes to obtain 62 candidates (defined as IBD key-nodes, Table S4) that represent genes predicted to influence IBD associated NF-κB regulation, which had also independently been identified as IBD associated genes or potential therapeutic targets.

Predicting drugs that may influence the IBD key-nodes

The PASS software package was used to predict drugs which may interact with IBD key-nodes: this software predicts the ability of a chemical structure to interact and influence the activity of defined molecular targets and biological activities.

The 62 key-nodes were translated into 46 PASS activities (Table S5). To identify compounds with potential for clinical re-positioning, the Top 200 drugs library was analysed to predict the probability that these established, and licenced agents may interfere with each PASS activity. A cumulative score was calculated across all 46 PASS activities for each drug. We also required that the drugs were predicted to be active against the PASS activity "Transcription factor NF κB inhibitor".

29 compounds achieved these criteria (Table 3); importantly, this table included several corticosteroids already used to treat IBD, supporting the validity of the discovery strategy.

The highest-ranked drug was a macrolide antibiotic: clarithromycin. This agent is of particular interest because macrolides have an established role in treating aseptic inflammatory conditions including chronic rhinosinusitis(Oakley et al., 2017) and panbronchiolitis(Lin et al., 2015) and because clarithromycin has previously been trialled in IBD with divergent outcomes(Leiper et al., 2008; Leiper et al., 2000). We, therefore, considered it to be an excellent candidate for strategic repurposing and have used clarithromycin as a paradigm molecule for the development of a mechanism-led drug validation pathway.

Clarithromycin suppresses stimulus-induced luciferase activity in primary cell cultures.

To validate the efficacy of clarithromycin as an inhibitor of NF-κB mediated transcription, primary cultures from the hTNF.LucBAC mouse, a transgenic line that expresses firefly luciferase under the control of the entire human *TNF* promoter(Minshawi et al., 2019), were used.

Luciferase activity was triggered by ligand binding to the TNF receptor and pattern recognition receptors including TLR4 (lipopolysaccharide), TLR5 (flagellin) and NOD2 (muramyl dipeptide, MDP) (Figures 2A-D) in peritoneal macrophages harvested from this mouse. When cells were pre-treated for 30 minutes with 10μM or 100μM clarithromycin, a dose-dependent reduction in luciferase activity was observed, independent of the stimulus applied.

The effect of clarithromycin on NF-κB activation in murine peritoneal macrophages was confirmed by isolating peritoneal macrophages from 4 WT mice, and treating them with 10μM clarithromycin or vehicle before stimulation with 1μg/ml LPS. Cells were fixed, stained for phosphorylated-p65 and quantified by flow cytometry. Median fluorescence intensity (MFI) increased on stimulation (p=0.03, ANOVA); co-administration of LPS and clarithromycin suppressed this response (p=0.008, Figure 2E).

Small intestinal organoids (enteroids) were established from hTNF.LucBAC mice to determine whether clarithromycin could also alter NF-κB responses in gastrointestinal epithelial cell cultures. Luciferase activity was detectable in these cultures in response to 100ng/mL TNF administration (Figure 3A and B). Luciferase activity was significantly suppressed by pre-treatment for 30 minutes with either 1μM (p=0.014) or 10μM (p=0.001) clarithromycin (Figure 3B and C).

Clarithromycin suppresses TNF-induced NF-κB(p65) shuttling in enteroids

To assess whether clarithromycin influenced NF-κB protein shuttling dynamics, enteroid cultures from reporter mice expressing p65-DsRedxp/IκBalpha-eGFP were established. This mouse expresses human p65-DsRedxp and human IκBalpha-eGFP fusion proteins. We used these organoids in live-cell confocal imaging studies to observe the nuclear translocation of p65 in real-time. Images were analysed using CellTracker software(Ashall et al., 2009), which allows painstaking quantification of nuclear shuttling of fluorescently labelled proteins.

Administration of 100ng/mL TNF-induced synchronised p65 translocation to the nucleus of cells within enteroids with a periodicity of approximately 50 minutes. This was observed as a highly damped shuttling response, with a single wave of synchronised nuclear translocation, followed by a second wave of partially synchronised translocation, after which further nuclear localisation occurred in an apparently stochastic fashion (Figure 4A and B and supplementary

video). When cultures were pre-treated with 10μM clarithromycin for 30 minutes, p65-DsRedxp nuclear translocation was markedly suppressed.

To quantify these events more precisely the mean area under the curve (AUC) during the first oscillatory wave (Figure 4D) was calculated, and demonstrated decreased nuclear intensity of p65-DsRed fluorescence in clarithromycin pre-treated enteroids (p=0.005). The time to peak nuclear fluorescence after 100ng/mL TNF administration was also quantified (figure 4E). In DMSO vehicle-treated cells, peak fluorescence occurred at a median time of 47.2 (IQR 41.0-47.2) minutes. This was not significantly different for clarithromycin treated enteroids, but there was significantly more cell-to-cell variability observed in clarithromycin treated than vehicle-treated cells (p<0.0001, figure 4E). To assess synchronisation of nuclear translocation, the time between peak fluorescence and median time for peak nuclear fluorescence was calculated for each cell (Figure 4F). This confirmed an 8-fold greater variation in timing for peak nuclear fluorescence in CLA treated enteroids compared to controls (p<0.0001), confirming that the synchronisation of p65 nuclear translocation was lost following exposure to CLA.).

Clarithromycin suppresses LPS-induced NF-κB (p65) DNA binding in-vivo

To determine whether the effects of clarithromycin on stimulus-induced NF-κB activity observed *in-vitro* also occurred *in-vivo*, 0.125mg/kg LPS was administered to groups of six C57BL/6 male mice by intraperitoneal injection, either with or without clarithromycin co-administration. This stimulus induces small intestinal epithelial cell shedding, regulated by both NF-κB1 and NF-κB2 signalling pathways(Williams et al., 2013).

LPS administration induced a 2-fold increase in p65 DNA binding, compared to saline vehicle control (p<0.001, 1-way ANOVA and Dunnett's posthoc test); pre-treatment with clarithromycin suppressed this effect by approximately 51% (p=0.007, Figure 5A).

Clarithromycin suppresses DSS-induced colitis

To determine whether clarithromycin affected murine colitis *in-vivo, c*larithromycin or vehicle were administered to mice receiving DSS to induce colitis. Animals received clarithromycin or vehicle daily for four days by oro-gastric gavage, after a four-day washout period 2.5% w/v DSS in drinking water *ad-libitum* was commenced for five days, followed by recovery for a further three days.

Mice co-administered DSS and clarithromycin lost significantly less weight than other groups (p=0.039, 1-way ANOVA and Dunnett's posthoc test, Figures 5B and 5C) and had lower compound histology scores (p=0.004, Figures 5D and 5F) and a higher number of surviving colonic crypts than mice treated with vehicle (p=0.017, Figure 5E); this suggests that clarithromycin at least partially ameliorates this model of colitis.

Clarithromycin suppresses TNF-induced NF-κB (p65) nuclear localisation in human enteroids

To determine whether the effects identified in murine primary culture and *in-vivo* experiments were also relevant to humans, passaged human ileal organoids from individuals with no evidence of IBD were pre-treated with 10μM clarithromycin or DMSO vehicle for 30 min before stimulation with 100ng/ml TNF. Paraformaldehyde fixed cultures were immunostained for p65, and the percentage of cells expressing nuclear-localised p65 was quantified. In untreated human enteroids, 0.6% (SEM 0.37) of cells demonstrated p65 nuclear localisation, administration of TNF induced a 57-fold increase in cells expressing nuclear p65 (33%, +/- 3.2 SEM, p<0.0001, 1-way ANOVA and Dunnett's posthoc test, N=6 per group). Pre-treatment with clarithromycin suppressed TNF-induced nuclear localisation of p65 to a level comparable with DMSO vehicle-treated enteroids. (1%, +/- 0.36 SEM, p<0.0001, Figure 6).

Discussion:

This article demonstrates that the macrolide antibiotic clarithromycin is a modifier of NF-κB signalling in the gastrointestinal tract. Identification of clarithromycin, using an *in-silico* screen

of licensed drugs, demonstrates how novel bioinformatics can be used to progress drug-repurposing, a strategy that has the potential to reduce the cost of future drug development. The SysmedIBD consortium integrated diverse skill sets to develop this approach which could be applied in different ways in the future. An identical bioinformatic analysis could be used to screen panels of small molecules to identify novel therapeutics for IBD. Similarly, the system could be adapted for use in other contexts where NF-κB signalling is of paramount importance or refocussed onto different signalling networks.

Our list of drugs predicted to influence IBD outcomes included several drugs in routine use for IBD, most prominently the corticosteroids, which are used to treat acute relapses of inflammatory bowel disease(Truelove and Witts, 1955; Turner et al., 2007). The analysis also identified sex hormones including medroxyprogesterone and estradiol which have been shown to modulate colitis(Armstrong et al., 2017), and colitis-associated adenoma development *in vivo*(Son et al., 2018); and non-steroidal anti-inflammatory drugs, which, in clinical practice, are identified as agents that exacerbate IBD(Long et al., 2016). The harmful effects of NSAIDs result from inhibition of constitutively expressed COX-1 in the gastrointestinal epithelium, causing epithelial damage and ulceration; inhibition of COX-2, which is upregulated at sites of inflammation is a well-established anti-inflammatory mechanism, which influences NF-κB signalling. The drug discovery approach deliberately included a bias for agents that alter NF-κB signalling; it is likely that NSAIDs have been selected because of this bias.

These observations demonstrate the importance of interdisciplinary working. The *in-silico* drug discovery model is a powerful tool to identify drugs that may be repurposed, but decisions about which agents to pursue for further analysis can only be made in the context of existing clinical literature.

Laboratory evaluation of clarithromycin aimed to demonstrate proof-of-principle that a drug identified by *in-silico* testing would demonstrate the predicted mechanism of action, and show efficacy *in-vivo*.

Our strategy has potential for development into a higher throughput compound screening system: for example, the hTNF.LucBAC macrophage assay can be performed in a 96-well plate format, and peritoneal macrophages are abundant, simple to extract and highly sensitive to stimulus. Reporter enteroids generated from hTNF.LucBAC mice allowed us to validate the findings seen in peritoneal macrophages in a relevant, untransformed epithelial model using comparable technology, but are unlikely to be amenable to high-throughput assay development due to the challenges (and cost) of maintaining a 3D culture in a small well in a culture plate.

The visualisation of p65.DsRed translocation between the nucleus and cytoplasm in enteric organoids is technically challenging, and not immediately scalable. One of the challenges that we persistently encountered was fluctuating fluorescence prior to stimulation with TNF, despite efforts to rest the cells prior to imaging. Unlike a monoculture of immune cells enteroids are a complex system with several cell types represented within the organoid structure. Whether this is due to paracrine secretion between different cells within the organoid structure, or is a factor related to organoid culture conditions is not possible to dissect currently. Our assays also demonstrated fundamental differences in NF-κB signalling dynamics compared to cancer cell lines(Harper et al., 2018; Nelson et al., 2004), with TNF-induced p65 oscillations being heavily damped in organoids. This observation demonstrates the value of untransformed primary culture; the mechanisms underlying these differences will be subject to further investigation.

The observation that intestinal NF-κB signalling is altered by clarithromycin *in-vivo* is in keeping with earlier work using cancer cell lines(Peng et al., 2014), but it is the first

demonstration that macrolides alter this signalling pathway in either untransformed enteroids or gastrointestinal mucosae *in vivo*.

Previous studies demonstrated that a non-antibiotic macrolide, CSY0073, influenced acute DSS colitis in C57BL/6 mice(Mencarelli et al., 2011), but clarithromycin had not been studied. Our murine experiments were complicated by the antibiotic effects of Clarithromycin. Murine models of colitis are known to vary dependent on animal house conditions and host enteric microbiota. Several strategies could have been adopted to help differentiate antibiotic and anti-inflammatory effects of clarithromycin, all of which arte flawed. Germ free mice and gnotobiotic mice have been used to impute impacts of gut microbiota in inflammatory bowel disease models, but they are flawed as immune systems development is divergent in germ free mice. Broad spectrum antibiotics have been usedin an attempt to eradicate commensal enteric bacteris, but no antibiotic combination will effectively achieve this goal, and its effect on the mycobiome and virome would be unquantifiable.

We preferred to adopt a consistent approach that was based on pre-exposure to the clarithromycin. The intention of this approach was to build evidence for the antibiotic effect of CLA by examining the impact of pre-treatment with CLA, and comparing to the anti-inflammatory effects of sustained CLA treatment. In the LPS administration experiment the timepoinrts are extremely short, therefore an antibiotic effect within the experimental period is highly unlikely to explain differences between CLA pretreated animals and animals administered CLA immediately before LPS. The antibiotic effect is a greater concern in the DSS experiment, but the inclusion of data from relevant control animals has allowed us to unpick the anti-inflammatory effect. Intriguingly the histological damage in mice pretreated with CLA was worse than that seen in the vehicle control mice, suggesting that the antibiotic effect in this model may, if anything, have the opposite effect to sustained CLA treatment.

The *in-vivo* studies rely on studying the whole organism and it was not feasible to separate epithelial and immune compartments during this study, this was one of the prime motivations for studying immune and epithelial models *in-vitro*

Our final validation was to characterise whether clarithromycin influenced human epithelial NF-κB signalling. We investigated this using a HeLa reporter cell-line model, which is fast, inexpensive, commercially available and could be adapted as a high throughput screening test (figure S2), but it is inferior to the hTNF.LucBAC mouse primary culture models as NF-κB signalling is dysregulated in many cancer cell lines. By generating human enteroids, clarithromycin's effect on a primary, untransformed human epithelial cell culture could be assessed. Unfortunately, the assay used for NF-κB activation in this model was necessarily less specific, but the results supported those obtained with other assays.

It was serendipitous that the highest-ranked agent identified for repurposing was a drug that had already been trialled in IBD. Importantly the outcomes of previous trials of clarithromycin in IBD have been heterogeneous, suggesting that there may be context-dependent factors that determine whether clarithromycin is useful in a group of patients.

Four published papers, and a conference abstract have reported the effect of clarithromycin in IBD: they all focussed on Crohn's disease and were predicated on an antibiotic effect of clarithromycin, either targeting intra-macrophage killing of *E. coli*(*Leiper et al., 2008; Leiper et al., 2000)* or attempting to eradicate *Mycobacterium avium paratuberculosis*(Goodgame et al., 2001; Graham et al., 1995; Selby et al., 2007).

Several factors may explain the discordant outcomes:

In all studies of clarithromycin's effect on IBD, patient inclusion was based on clinical definitions of active IBD and response assessed by clinical outcome measures. These measures lack objectivity and would not be acceptable endpoints or selection criteria for a current study.

Selby(Selby et al., 2007) and Goodgame(Goodgame et al., 2001). assessed the long-term effect of bacterial eradication; any anti-inflammatory effect would have been lost during the prolonged follow-up period before the primary endpoint was assessed.

Leiper *et al* examined an earlier timepoint when anti-inflammatory effects, could have been observed, but were not the focus of the study. Two separate cohorts of patients with clinically active Crohn's disease were recruited from a single centre; in the first study clarithromycin appeared to improve patient outcomes, but the same was not observed during the second study.

At the time, the divergent outcomes were explained by the small size of the initial study, and the relatively soft criteria for inclusion of patients with active inflammatory bowel disease. These explanations may still be valid, but an alternative hypothesis is that a sub-group of patients with active disease may respond to clarithromycin. One of the motivations for investigating existing drugs during this study was specifically to identify agents that have equivocal evidence based on traditional trials but that have evidence for an untested mechanism of action.

The current study confirms that in addition to its antibiotic effect, clarithromycin has anti-inflammatory properties, which are relevant to gastrointestinal epithelia. Further carefully designed clinical studies will be needed to test the anti-inflammatory effects of treatment with clarithromycin.

Earlier discordant trial results raise questions about trial design and patient selection. In the current era of precision medicine, it is important that patients are carefully selected for treatments, and that agents with previous dichotomous clinical trial results are revisited. To effectively review drugs for precision use, their mechanisms of action need to be understood. This study has helped us to understand how clarithromycin affects NF-κB signalling dynamics,

and we hypothesise that it should be possible to select a group of clarithromycin-responsive patients based on their NF-κB signalling status.

Our consortium has recently shown that patients with IBD cluster into several different cohorts based on a dynamic measure of NF-κB responses in peripheral blood monocyte derived macrophages(Papoutsopoulou et al., 2019). We hypothesise that, by using this new measure of NF-κB activity, it will be possible to identify IBD patients most likely to respond to NF-κB targeted therapy in the form of clarithromycin, and thereby leverage a precision medicine trial.

In conclusion, our findings strongly suggest that clarithromycin may be a viable, anti-inflammatory therapeutic agent for IBD. In order to progress to a personalised medicine trial of clarithromycin in IBD a partner diagnostic test which can demonstrate altered NF-κB dynamics in patients' peripheral blood monocyte-derived macrophages is under development(Papoutsopoulou et al., 2019), once established this will be used to inform a personalised drug repurposing trial for clarithromycin in IBD.

Conflicts of Interest:

VDS is a shareholder and director of GeneXplain GmbH

AK is a shareholder and director of LifeGlimmer GmbH

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Author Contributions:

KL performed experiments, acquired original data, analysed data and drafted part of the manuscript. SP performed experiments, acquired original data, analysed data and drafted part of the manuscript. ES performed experiments and acquired original data. PS developed analytical tools, analysed data and drafted part of the manuscript. FB analysed data and

drafted part of the manuscript. LM analysed data and drafted part of the manuscript. MK developed analytical pathways and analysed data. HE performed experiments, acquired original data and analysed data. DS supported imaging experiments and reviewed the manuscript. MW devised the project and contributed to funding applications. CD supported organoid work and reviewed the manuscript. BC contributed to funding applications and reviewed the manuscript. VP developed analytical tools and analysed data. VMdS contributed to funding applications and supported the development of analytical pathways. AK contributed to funding applications, supported the development of novel analytical tools, performed data analyses and contributed to the drafting of the manuscript. WM contributed to funding applications and study design, reviewed the manuscript and supported laboratory work. DMP reviewed the manuscript and supported laboratory work. CP contributed to funding applications, designed the study, reviewed the manuscript and supported laboratory work. MB designed the research study, conducted experiments, analysed data, drafted the manuscript and coordinated the project.

Acknowledgements: This work was supported by the European Union Seventh Framework Programme [FP7/2012–2017] under the SysmedIBD grant, agreement no. 305564

Figure Legends

Figure 1: Schematic representation of the bioinformatic approach to identifying drugs with the potential to modulae IBD and NF-κB signalling.

Figure 2. A-D: Luciferase activation curves for peritoneal macrophages extracted from HTNF.LucBAC mice stimulated with 10ng/mL LPS (**A**), 40 ng/mL TNF (**B**), 10µg/mL MDP (**C**) or 500ng/ml flagellin (**D**). Solid lines indicate cells response of pre-treated with drug vehicle (DMSO), dashed and dotted lines responses generated from cells pre-treated with 10µM or 100 µM clarithromycin, respectively. **E:** Median fluorescence intensity for anti-phopsho-p65 antibody stained peritoneal macrophages from C57BL/6 mice either unstimulated or stimulated with LPS and pre-treated with 10µM clarithromycin or DMSO vehicle. N=4 mice. Statistically significant differences tested by 1-way ANOVA and Dunnett's post hoc test.

Figure 3: Representative luciferase activation curves for enteroids derived from HTNF.LucBAC mice either unstimulated (**A**) or stimulated with 100ng/mL TNF (**B**), and without pre-treatment (solid line) or 30 min pre-treatment with, DMSO vehicle (dashed line), 1µM clarithromycin (dotted line) or 10µM clarithromycin (dotted and dashed line). **C:** Area under the curve (AUC) calculations for the same experiment. N=3. Statistically significant differences tested by 2-way ANOVA and Dunnett's posthoc test.

Figure 4 A: Representative images of bright field (upper panels) and red channel (lower panels) images of dynamic, live-cell imaging studies of enteroids derived from p65-DsRedxp/ IκBalpha-eGFP mice, either untreated, treated with clarithromycin alone, treated with 100ng/mL TNF alone, or pre-treated with 10µM clarithromycin and subsequently stimulated with TNF. **B and C:** Relative nuclear red fluorescence curves for individual cells (grey lines), mean (solid red line) and 1 SD above and below the mean (dashed red lines) over time. Cells pre-treated with DMSO vehicle **(B)** or clarithromycin **(C)** at time -35 min and stimulated with

TNF at time 0 min. **D:** Area under the curve calculations for individual cells between time 0 and time 90 min for panels B and C. Statistically significant differences tested by Mann-Whitney U test. **E:** Time to peak fluorescence, post-TNF stimulation for individual cells, statistically significant differences tested by Mann-Whitney U test. **F:** Distance of individual cells peak fluorescence from the median value, statistically significant differences tested by Mann-Whitney U test. N=88 vehicle pre-treated, 62 clarithromycin pre-treated cells for panels D-F, lines represent median and IQR for these panels.

Figure 5A: Relative p65 DNA binding activity in whole-cell lysates from proximal small intestine of C57BL/6 mice pretreated for three days with 50mg/kg clarithromycin or saline vehicle, and subsequently injected i.p. with 0.125mg/kg LPS or vehicle. N=5-6. **B-F:** Effect of clarithromycin on outcomes of DSS colitis in C57BL/6 mice. **B:** Weight loss plotted over time. **C:** Area under the curve analysis of weight loss. **D:** Histology severity scores. **E:** Number of surviving crypts per colonic circumference. **F:** Representative photomicrographs of the colonic mucosa of DSS treated mice co-treated with saline vehicle or 10mg/kg clarithromycin by oro-gastric gavage. N=9-10. Statistically significant differences tested by 1-way ANOVA and Dunnett's post hoc test in all panels.

Figure 6A: Representative photomicrographs of human ileal enteroids either unstimulated or stimulated with 100ng/ml TNF, and either co-administered DMSO vehicle or 10µM clarithromycin and immunostained for total p65. **B:** Quantification of nuclear p65 staining of human enteroids. Statistical testing by Kruskal-Wallis 1-way ANOVA and Dunn's post hoc, N=6.

Tables:

ID	Gene symbol
ENSG00000156273	*BACH1*
ENSG00000164330	*EBF1*
ENSG00000134954	*ETS1*
ENSG00000175592	*FOSL1*
ENSG00000154727	*GABPA*
ENSG00000104064	*GABPB1*
ENSG00000125347	*IRF1*
ENSG00000168310	*IRF2*
ENSG00000137265	*IRF4*
ENSG00000128604	*IRF5*
ENSG00000185507	*IRF7*
ENSG00000140968	*IRF8*
ENSG00000213928	*IRF9*
ENSG00000177606	*JUN*
ENSG00000171223	*JUNB*
ENSG00000130522	*JUND*
ENSG00000109320	*NFKB1*
ENSG00000077150	*NFKB2*
ENSG00000162924	*REL*
ENSG00000173039	*RELA*
ENSG00000104856	*RELB*
ENSG00000159216	*RUNX1*
ENSG00000020633	*RUNX3*
ENSG00000269404	*SPIB*

Table 1: Transcription factors predicted to contribute to NF-κB regulatory cascades by MEALR analysis

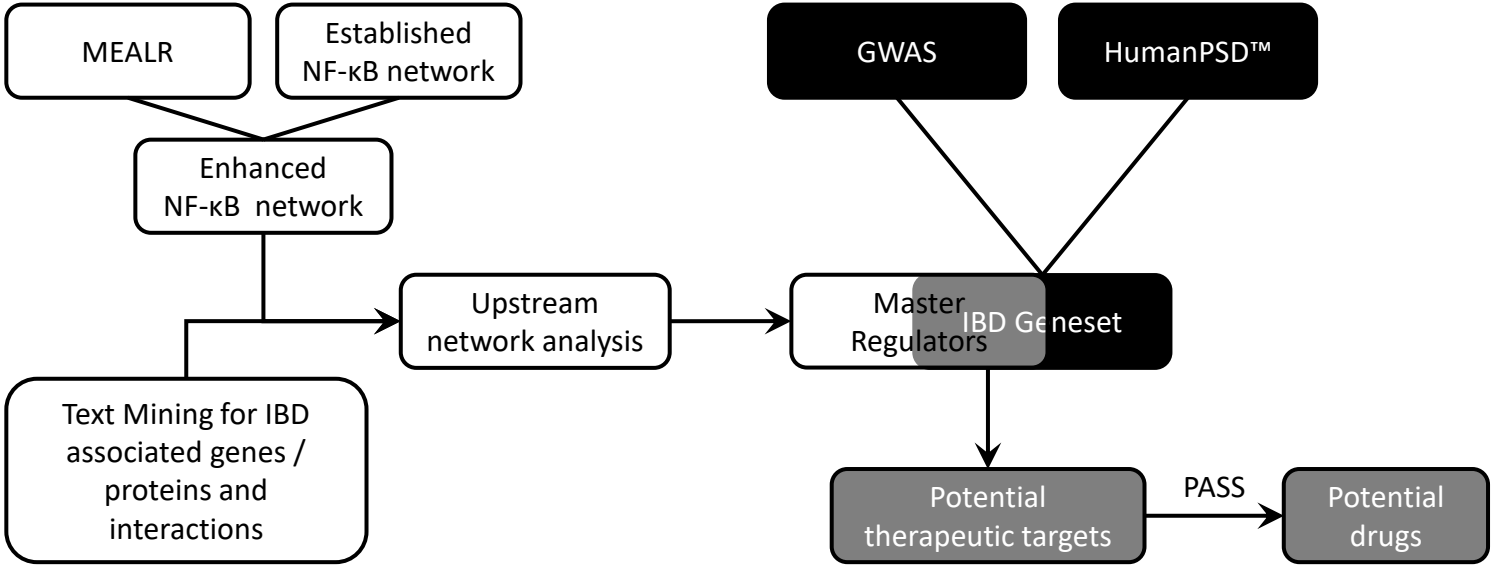
ID	Gene symbol	# consensus NF-κB/RelA sites within 10kb from gene
ENSG00000005339	*CREBBP*	1
ENSG00000015475	*BID*	2
ENSG00000030110	*BAK1*	1
ENSG00000034152	*MAP2K3*	1
ENSG00000049759	*NEDD4L*	3
ENSG00000051382	*PIK3CB*	1
ENSG00000051523	*CYBA*	1
ENSG00000069399	*BCL3*	2
ENSG00000077150	*NFKB2*	2
ENSG00000081059	*TCF7*	3
ENSG00000082701	*GSK3B*	1
ENSG00000083799	*CYLD*	1
ENSG00000084676	*NCOA1*	2
ENSG00000099341	*PSMD8*	1
ENSG00000100324	*TAB1*	2
ENSG00000100365	*NCF4*	2
ENSG00000100387	*RBX1*	1
ENSG00000101849	*TBL1X*	1
ENSG00000102871	*TRADD*	1
ENSG00000104365	*IKBKB*	2
ENSG00000104825	*NFKBIB*	1
ENSG00000104856	*RELB*	2
ENSG00000105647	*PIK3R2*	1
ENSG00000107263	*RAPGEF1*	3
ENSG00000109320	*NFKB1*	2
ENSG00000109332	*UBE2D3*	2
ENSG00000110330	*BIRC2*	1
ENSG00000111186	*WNT5B*	1
ENSG00000112062	*MAPK14*	1
ENSG00000115415	*STAT1*	2
ENSG00000116473	*RAP1A*	2
ENSG00000116701	*NCF2*	1
ENSG00000118260	*CREB1*	1
ENSG00000118503	*TNFAIP3*	2
ENSG00000119487	*MAPKAP1*	3
ENSG00000121879	*PIK3CA*	1
ENSG00000124486	*USP9X*	1
ENSG00000125084	*WNT1*	1
ENSG00000125347	*IRF1*	1
ENSG00000127191	*TRAF2*	2
ENSG00000127666	*TICAM1*	1
ENSG00000131323	*TRAF3*	5
ENSG00000131508	*UBE2D2*	1

ENSG00000134070	*IRAK2*	2
ENSG00000136689	*IL1RN*	1
ENSG00000136807	*CDK9*	1
ENSG00000136810	*TXN*	1
ENSG00000137275	*RIPK1*	2
ENSG00000141510	*TP53*	1
ENSG00000142453	*CARM1*	1
ENSG00000144802	*NFKBIZ*	2
ENSG00000145675	*PIK3R1*	1
ENSG00000146232	*NFKBIE*	1
ENSG00000148053	*NTRK2*	1
ENSG00000148737	*TCF7L2*	1
ENSG00000150991	*UBC*	1
ENSG00000154589	*LY96*	1
ENSG00000157764	*BRAF*	1
ENSG00000161011	*SQSTM1*	1
ENSG00000162736	*NCSTN*	1
ENSG00000162924	*REL*	2
ENSG00000163932	*PRKCD*	3
ENSG00000164327	*RICTOR*	1
ENSG00000166167	*BTRC*	1
ENSG00000168036	*CTNNB1*	1
ENSG00000169967	*MAP3K2*	1
ENSG00000170315	*UBB*	1
ENSG00000171552	*BCL2L1*	2
ENSG00000171608	*PIK3CD*	2
ENSG00000172936	*MYD88*	1
ENSG00000173039	*RELA*	1
ENSG00000174130	*TLR6*	1
ENSG00000177606	*JUN*	1
ENSG00000183207	*RUVBL2*	1
ENSG00000185338	*SOCS1*	1
ENSG00000185507	*IRF7*	1
ENSG00000185627	*PSMD13*	1
ENSG00000186197	*EDARADD*	1
ENSG00000196470	*SIAH1*	1
ENSG00000197153	*HIST1H3J*	2
ENSG00000197409	*HIST1H3D*	3
ENSG00000197442	*MAP3K5*	3
ENSG00000198400	*NTRK1*	1
ENSG00000205155	*PSENEN*	2
ENSG00000213281	*NRAS*	1
ENSG00000226979	*LTA*	4
ENSG00000227507	*LTB*	3
ENSG00000232810	*TNF*	4
ENSG00000243414	*TICAM2*	2
ENSG00000263528	*IKBKE*	3

Table 2: NF-κB target genes identified by MEALR to be involved in regulatory cascades

Ranking	Drug
1	Clarithromycin
2	Budesonide
3	Digoxin
4	Dexamethasone
5	Triamcinolone acetonide
6	Methylprednisolone
7	Prednisone
8	Azithromycin
9	Medroxyprogesterone
10	Estradiol
11	Nystatin
12	Progesterone
13	Albuterol
14	Ibuprofen
15	Dicyclomine
16	Naproxen
17	Nabumetone
18	Propranolol
19	Metoprolol
20	Atenolol
21	Acetaminophen
22	Phentermine
23	Divalproex
24	Gabapentin
25	Diclofenac
26	Lisdexamfetamine
27	Pregabalin
28	Methocarbamol
29	Metformin

Table 3: Drugs predicted to influence IBD.


MEALR
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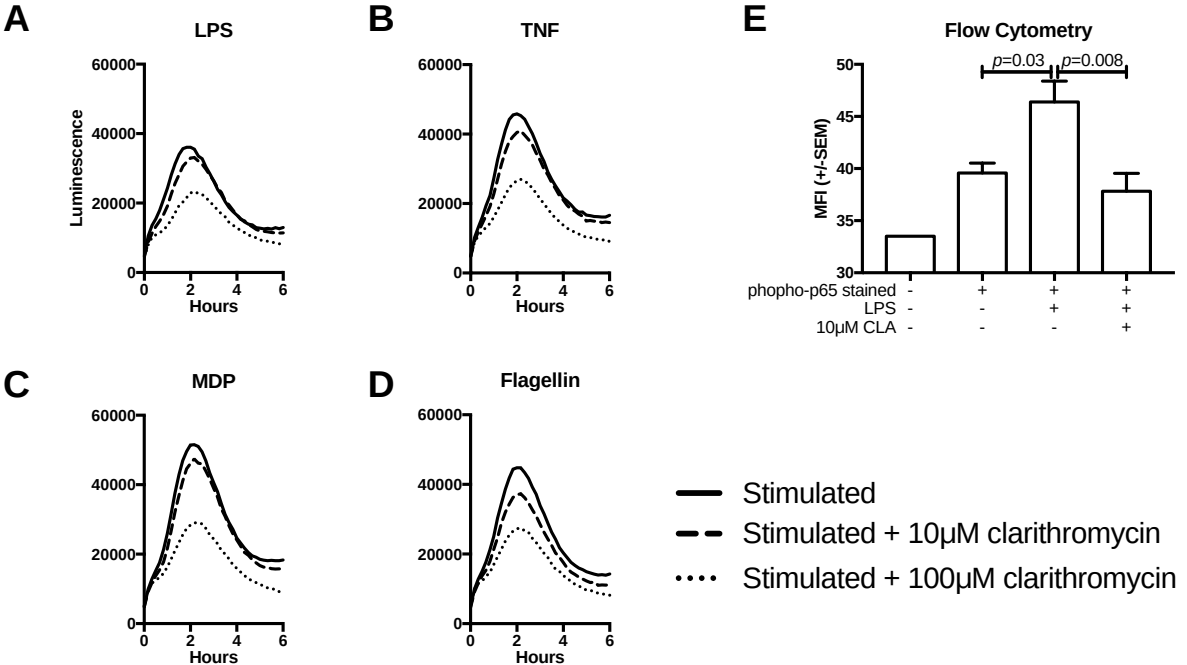
PASS
Potential drugs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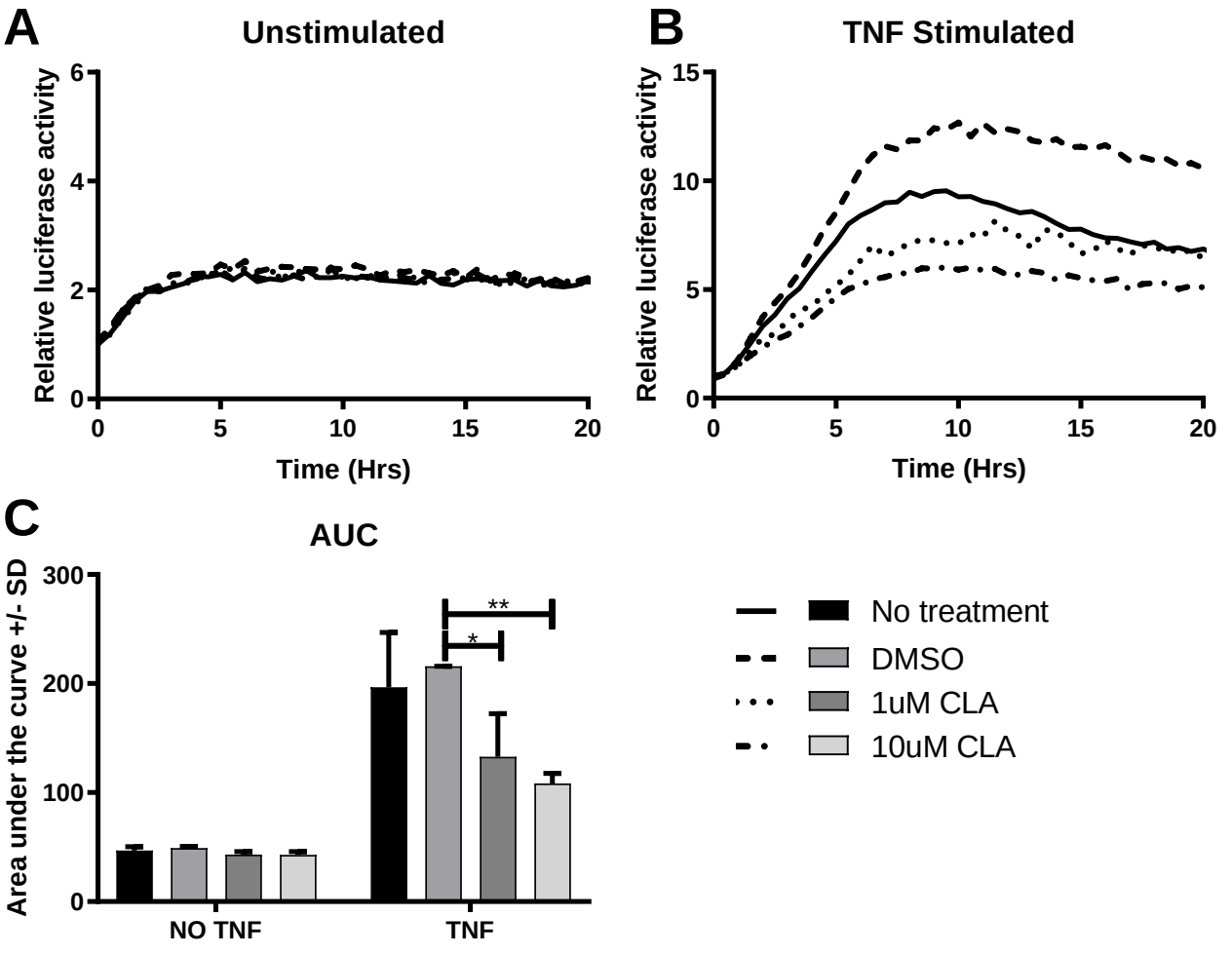
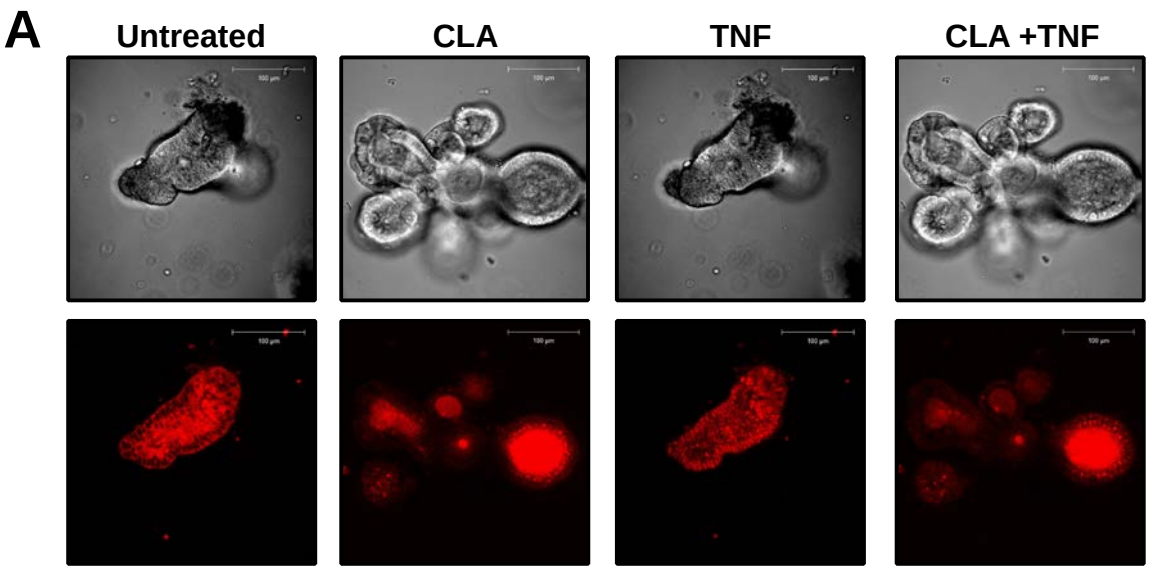
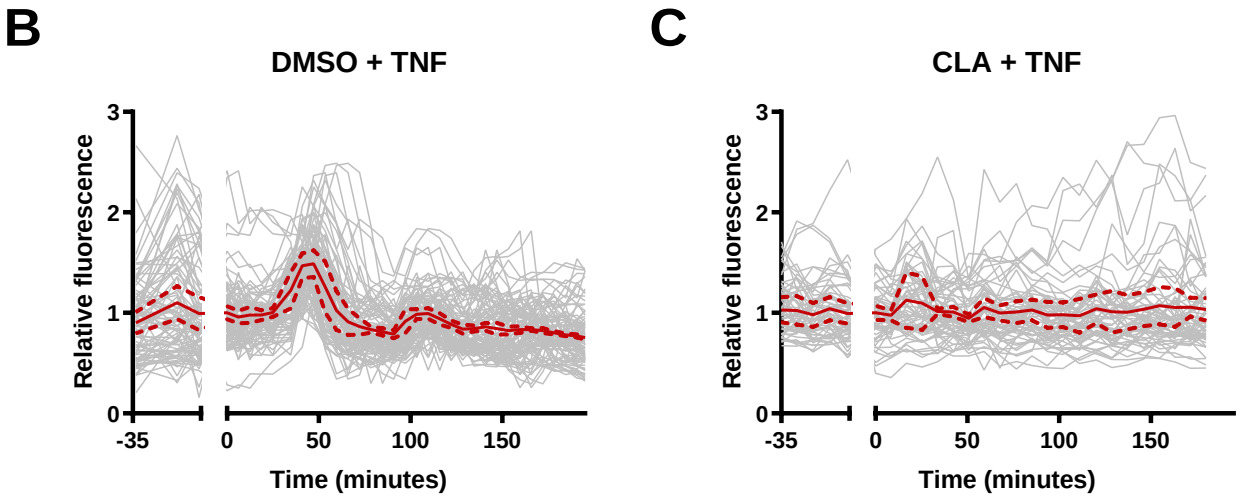
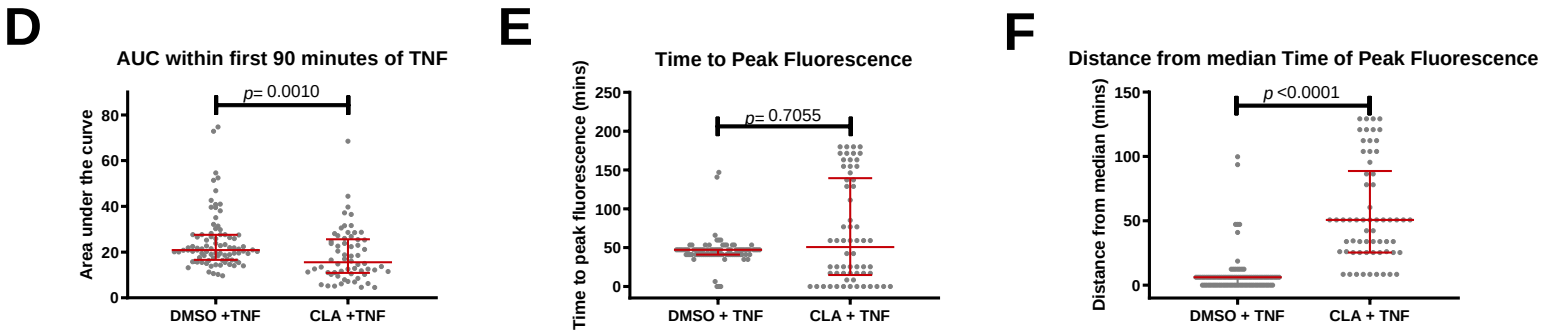
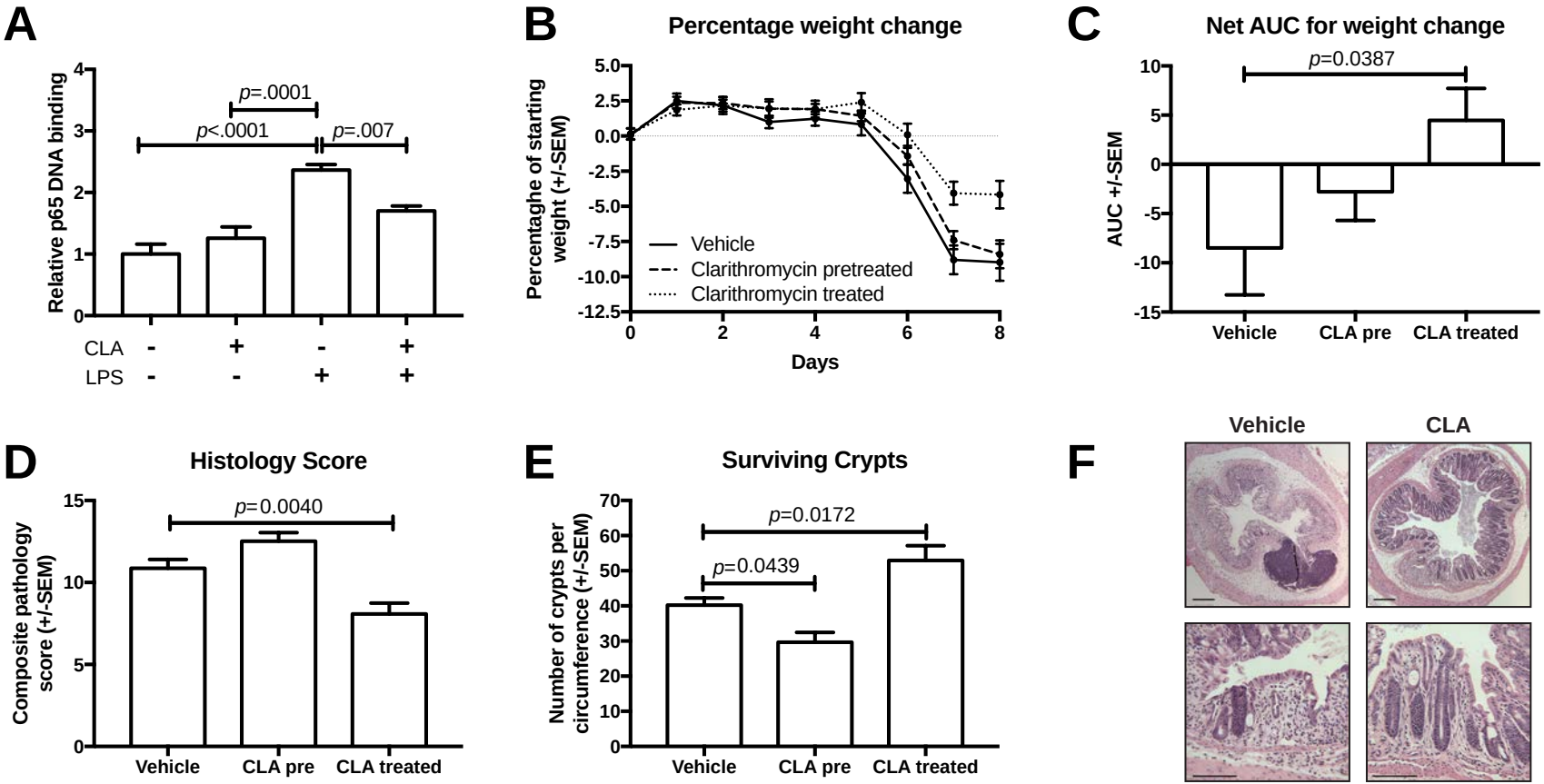
TNF
60000
40000
20000
0
0
2
4
6
Hours
E
Flow Cytometry
p=0.03
p=0.008
MFI (+/-SEM)
50
45
40
35
30
phopho-p65 stained - + + +
LPS - - + +
10μM CLA - - - +
C
MDP
60000
40000
20000
0
0
2
4
6
Hours
D
Flagellin
60000
40000
20000
0
0
2
4
6
Hours
Stimulated
Stimulated + 10μM clarithromycin
Stimulated + 100μM clarithromycin

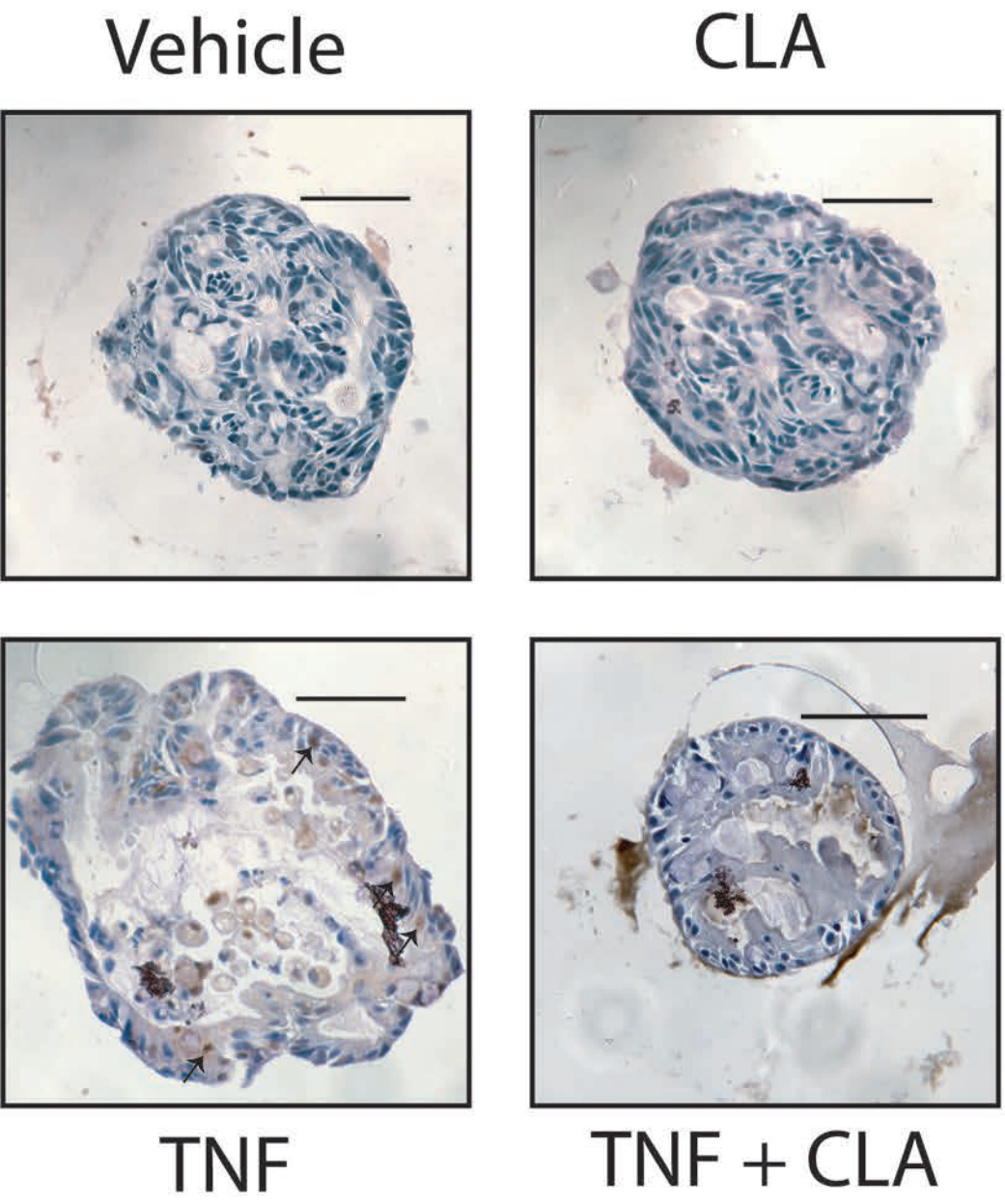

A
Unstimulated
Relative luciferase activity
0
2
4
6
0
5
10
15
20
Time (Hrs)
B
TNF Stimulated
Relative luciferase activity
0
5
10
15
0
5
10
15
20
Time (Hrs)
C
AUC
Area under the curve +/- SD
0
100
200
300
**
*
NO TNF
TNF
No treatment
DMSO
1uM CLA
10uM CLA

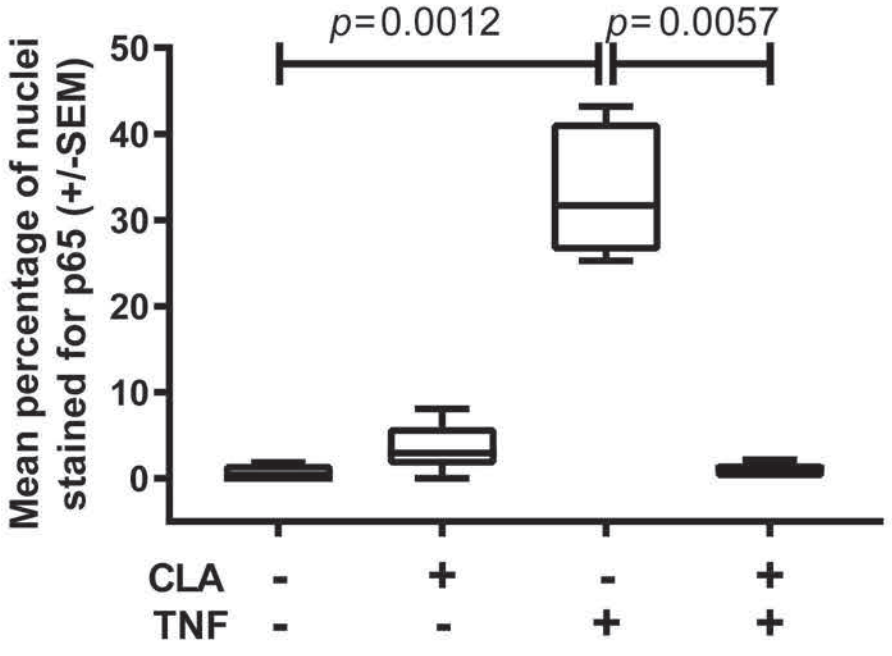

A
Untreated
CLA
TNF
CLA +TNF


B
DMSO + TNF
Relative fluorescence
Time (minutes)
C
CLA + TNF
Relative fluorescence
Time (minutes)


D
AUC within first 90 minutes of TNF
p= 0.0010
Area under the curve
DMSO +TNF
CLA +TNF
E
Time to Peak Fluorescence
p= 0.7055
Time to peak fluorescence (mins)
DMSO + TNF
CLA + TNF
F
Distance from median Time of Peak Fluorescence
p <0.0001
Distance from median (mins)
DMSO + TNF
CLA + TNF


A
Relative p65 DNA binding
p=.0001
p<.0001
p=.007
CLA - + - +
LPS - - + +
B
Percentage weight change
Percentaghe of starting weight (+/-SEM)
Vehicle
Clarithromycin pretreated
Clarithromycin treated
Days
C
Net AUC for weight change
p=0.0387
AUC +/-SEM
Vehicle
CLA pre
CLA treated
D
Histology Score
p=0.0040
Composite pathology score (+/-SEM)
Vehicle
CLA pre
CLA treated
E
Surviving Crypts
p=0.0172
p=0.0439
Number of crypts per circumference (+/-SEM)
Vehicle
CLA pre
CLA treated
F
Vehicle
CLA


Vehicle
CLA
TNF
TNF + CLA


p=0.0012
p=0.0057
Mean percentage of nuclei stained for p65 (+/-SEM)
50
40
30
20
10
0
CLA - + - +
TNF - - + +

Supplementary figures

Supplementary figure S1: Schematic of the transcriptional feedback loops sought by our analysis. Upon activation through upstream signalling cascades the transcriptional regulator NF-kappa-B/RelA (and cooperating transcription factors) control expression of target genes which may themselves play a role in signalling cascades regulating the activity of NF-kappa-B/RelA thereby establishing a positive or negative feedback loop depending on whether NF-kappa-B/RelA enhances or interferes with the transcription of respective target genes. **B:** More detailed illustration of identified feedback loops. Using consensus NF-kappa-B/RelA binding sites collected from 10 ChIP-seq experiments we analysed their genomic locations with respect to nearby potential target genes which were known components of relevant pathways and/or transcription factors whose motifs played a role for target sequence recognition as inferred by MEALR. Details of the compiled and analysed data are exemplified for pathway target genes TNF, LTA and LTB on chromosome 6 and for the cooperating transcription factor JUN on chromosome 1. The consensus peak density presentation was calculated using the CMplot package. The detailed views of genomic regions were created using the genome browser of the geneXplain platform.

Supplementary Video: Representative timelapse confocal video of red channel images of dynamic, live-cell imaging studies of enteroids derived from p65-DsRedxp/ IκBalpha-eGFP mice, either treated with 100ng/mL TNF alone, or pre-treated with 10μM clarithromycin and subsequently stimulated with TNF.

Supplementary Figure S2: Relative luciferase activity in unstimulated HeLa cells treated with DMSO vehicle (open bar), 1uM (hatched bar) or 10uM (solid bar) clarithromycin. B: Relative luciferase activity

in TNF stimulated HeLa cells treated with DMSO vehicle, 1uM or 10uM CLA. * denotes p<.05, ****p<.0001, by 2-way ANOVA and Dunnett's posthoc test.

Supplementary Table S1: NF-κB co-operating transcription factors identified by MEALR

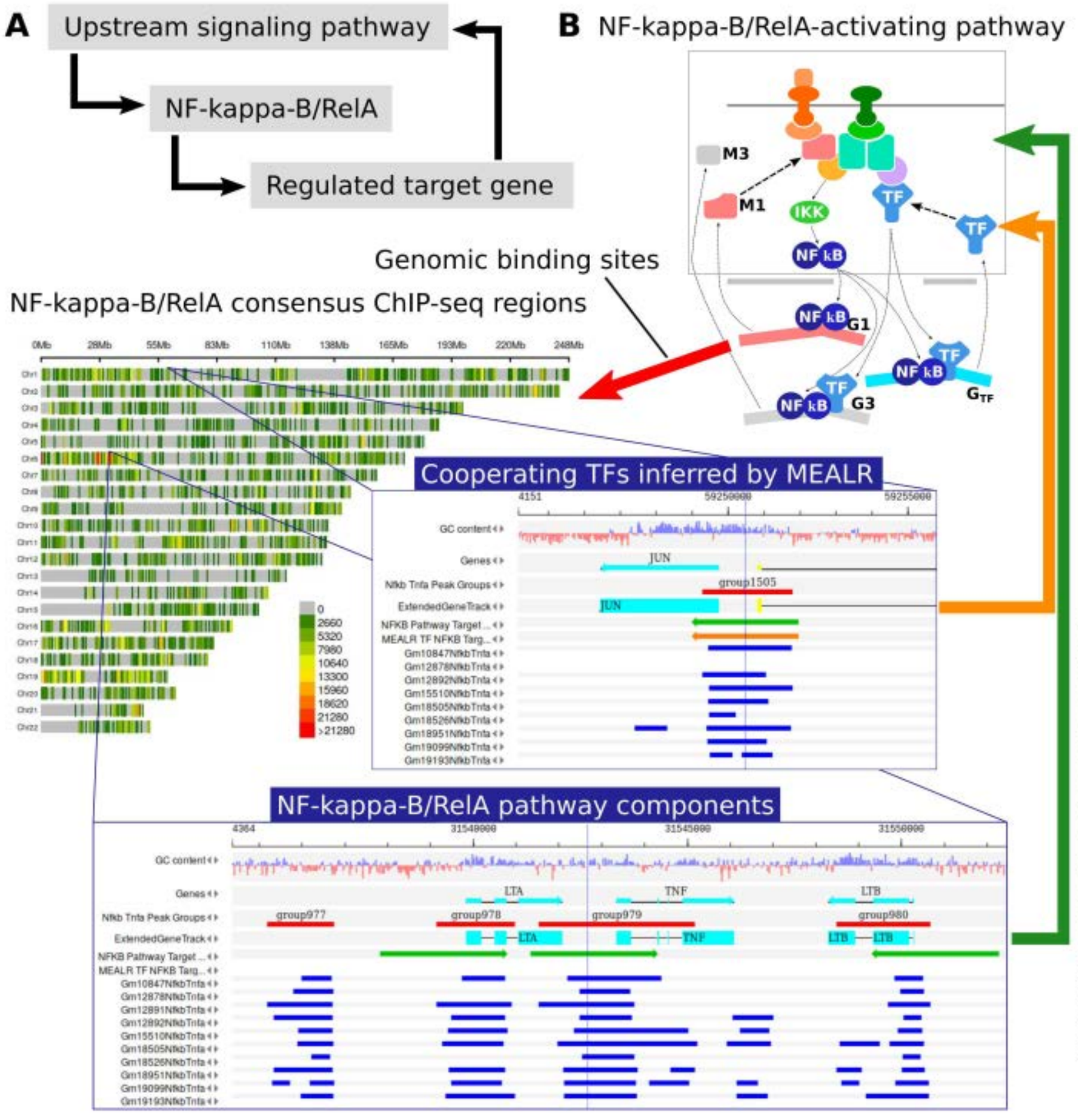
Supplementary Table S2: Interactions between genes and or proteins identified by text mining algorithm

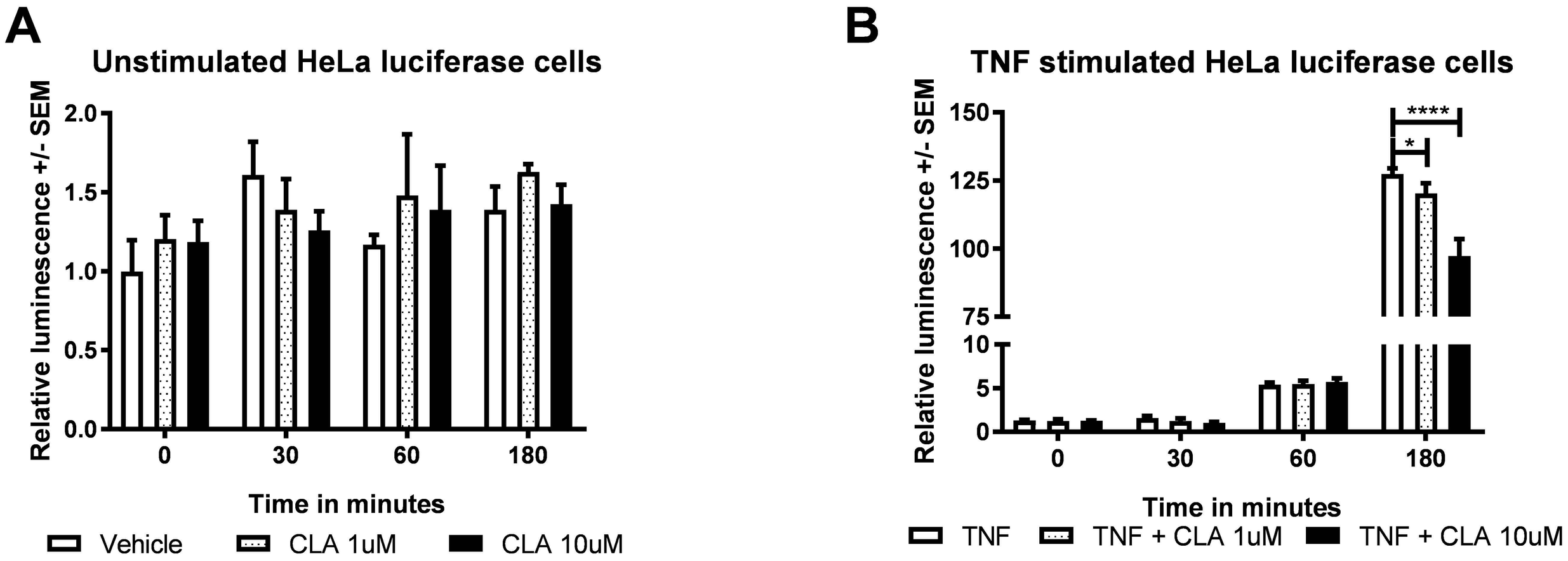
Supplementary Table S3: Controlling node genes that may regulate signalling activity on the NF-κB network

Supplementary Table S4: IBD target genes, with source of data

Supplementary Table S5: List of IBD key-nodes, potential therapeutic targets for IBD

Supplementary Table S6: IBD key-nodes and their associated PASS activities


A
Upstream signaling pathway
NF-kappa-B/RelA
Regulated target gene
B
NF-kappa-B/RelA-activating pathway
M3
M1
IKK
TF
TF
NF kB
NF kB
G1
NF kB
TF
NF kB
TF
G3
G_TF
Genomic binding sites
NF-kappa-B/RelA consensus ChIP-seq regions
0Mb
28Mb
55Mb
83Mb
110Mb
138Mb
165Mb
193Mb
220Mb
248Mb
0
2660
5320
7980
10640
13300
15960
18620
21280
>21280
Cooperating TFs inferred by MEALR
4151
59250000
59255000
GC content
Genes
JUN
Nfkb Tnfa Peak Groups
group1505
ExtendedGeneTrack
JUN
NFKB Pathway Target ...
MEALR TF NFKB Targ...
Gm10847NfkbTnfa
Gm12878NfkbTnfa
Gm12892NfkbTnfa
Gm15510NfkbTnfa
Gm18505NfkbTnfa
Gm18526NfkbTnfa
Gm18951NfkbTnfa
Gm19099NfkbTnfa
Gm19193NfkbTnfa
NF-kappa-B/RelA pathway components
4364
31540000
31545000
31550000
GC content
Genes
LTA
TNF
LTB
Nfkb Tnfa Peak Groups
group977
group978
group979
group980
ExtendedGeneTrack
LTA
TNF
LTB
LTB
NFKB Pathway Target ...
MEALR TF NFKB Targ...
Gm10847NfkbTnfa
Gm12878NfkbTnfa
Gm12891NfkbTnfa
Gm12892NfkbTnfa
Gm15510NfkbTnfa
Gm18505NfkbTnfa
Gm18526NfkbTnfa
Gm18951NfkbTnfa
Gm19099NfkbTnfa
Gm19193NfkbTnfa
NF-kappa-B/RelA consensus targets


A
Unstimulated HeLa luciferase cells
Relative luminescence +/- SEM
2.0
1.5
1.0
0.5
0.0
0
30
60
180
Time in minutes
Vehicle
CLA 1uM
CLA 10uM
B
TNF stimulated HeLa luciferase cells
Relative luminescence +/- SEM
150
125
100
75
10
5
0
****
*
0
30
60
180
Time in minutes
TNF
TNF + CLA 1uM
TNF + CLA 10uM

ɔtion factors identified by MEALR

Site model ID
V$BACH1_01
V$BACH2_01
VAML_Q6,VPEBP_Q6
V$DEAF1_02
V$COE1_Q6
V$ELF1_Q6
V$ELK1_01,V$ELK1_02
V$CETS1P54_03,V$ETS1_B,V$ETS_B
V$ETS_B
V$AP1_01
V$AP1_01
V$AP1_01,V$FRA1_Q5,V$FRA1_Q6
V$GADP_01
V$GABPBETA_Q3,V$GADP_01
V$IRF1_01,V$IRF1_Q6,V$IRF1_Q6_01,V$IRF_Q6,V$IRF_Q6_01
V$IRF2_01,V$IRF_Q6,V$IRF_Q6_01
VIRF_Q6,VIRF_Q6_01
VIRF_Q6,VIRF_Q6_01
VIRF_Q6,VIRF_Q6_01
V$IRF_Q6
VIRF_Q6,VIRF_Q6_01
V$ICSBP_Q6,V$IRF8_Q6,VIRF_Q6,VIRF_Q6_01
VIRF_Q6_01,VISRE_01
V$AP1_01
V$AP1_01,V$JUNB_Q6
V$AP1_01,V$JUND_Q6
V$MAFK_Q3,V$NFE2_01,V$NFE2_Q6
V$NFE2_01,V$NFE2_Q6
V$NFKAPPAB50_01,V$NFKAPPAB_01,V$NFKB_C,V$NFKB_Q6,V$NFKB_Q6_01,V$P50P50_Q3,V$P50RELAP65
V$NFKB_Q6_01,V$RELBP52_01
V$CREL_01,V$CREL_Q6
V$NFKAPPAB65_01,V$NFKAPPAB_01,V$NFKB_Q6_01,V$P50RELAP65_Q5_01,V$RELA_Q6,V$RELBP52_01
V$RELBP52_01
V$AML1_Q4,V$AML1_Q6,VAML_Q6,VPEBP_Q6
V$AML3_Q6,V$AML_Q6,V$OSF2_Q6,V$PEBP_Q6
V$AML2_01,V$AML_Q6,V$PEBP_Q6
V$PU1_Q4,V$PU1_Q6,V$SPI1_01
V$SPIB_01

Selected in #ChIP-seq data sets
9
10
9
10
9
10
10
10
10
10
9
10
9
10
10
10
9
10
10
9
10
10
9
10
9
9
10
9
10
10
10
10
10
10
10
10
10
10

Table S2: Interactions between genes and/or proteins identified by text mining algorithm

Gene Symbol 1	Gene Symbol 2	Type of interaction	Mouse / Human
Abl	c-Jun	Process	Human
AKT-1	ASK1	Process	Human
ASK1	MKK6	Process	Human
Caspase-8	parkin	Process	Human
ERK2	TAB1	Process	Human
IKK	NF-kappaB1	Process	Human
JNK1	JNK1alpha1	Process	Human
JNK1	JNK2	Process	Human
JNK1alpha1	TAB1	Process	Human
JNK2	MKK7	Process	Human
MEK1	MEKK1	Process	Human
MEKK1	STAT3	Process	Human
MKK6	TRAF2	Process	Human
MSK1	p38alpha	Process	Human
MyD88	TLR9	Process	Human
NF-kappaB1	NF-kappaB1-p50	Association	Human
NF-kappaB1	p50	Association	Human
NF-kappaB1	RelA-p65	Association	Human
NF-kappaB1-p50	p50	Association	Human
NF-kappaB1-p50	RelA-p65	Association	Human
Nod2	TRAF2	Association	Human
Nod2	ubiquitin	Association	Human
parkin	ubiquitin	Association	Human
TAK1	TAK1a	Association	Human
TAK1a	TRAF2	Association	Human
TAK1a	ubiquitin	Association	Human
JIP1	JNK1	Process	Mouse
PKCzeta	proCaspase-3	Process	Mouse
26S proteasome	IkappaB-alpha	Process	Both
26S proteasome	p105	Dissociation	Both
26S proteasome	p50	Dissociation	Both
26S proteasome	p50	Process	Both
26S proteasome	RelA-p65	Process	Both
26S proteasome	ubiquitin	Dissociation	Both
26S proteasome	ubiquitin	Process	Both
A20	IKK	Process	Both
A20	IKK-beta	Process	Both
A20	RIP	Dissociation	Both
A20	TRADD	Dissociation	Both
A20	TRAF2	Dissociation	Both
A20	ubiquitin	Dissociation	Both
Abl	Caspase-8	Dissociation	Both
Abl	IkappaB-alpha	Process	Both
acetyl-CoA	carm1	Process	Both
acetyl-CoA	CBP	Process	Both
acetyl-CoA	CoA	Process	Both

acetyl-CoA	histone H3	Process	Both
acetyl-CoA	p50	Process	Both
acetyl-CoA	RelA-p65	Process	Both
acetyl-CoA	SRC-1	Process	Both
ASK1	MKK4	Process	Both
ASK1	TNF-alpha	Process	Both
ASK1	TNFR1	Process	Both
ASK1	TRADD	Process	Both
ASK1	TRAF2	Process	Both
ASK1	Trx1	Association	Both
ASK1	Trx1	Dissociation	Both
Bak	Bid	Association	Both
Bak	Bid	Process	Both
Bak	Cytochrome C	Process	Both
Bak	tBid	Association	Both
Bak	tBid	Process	Both
Bid	Caspase-8	Dissociation	Both
Bid	Cytochrome C	Process	Both
Bid	tBid	Association	Both
Bid	tBid	Dissociation	Both
Bid	tBid	Process	Both
carm1	CBP	Association	Both
carm1	CBP	Process	Both
carm1	Cdk9	Association	Both
carm1	Cdk9	Process	Both
carm1	CoA	Process	Both
carm1	cyclinT1	Association	Both
carm1	cyclinT1	Process	Both
carm1	histone H3	Process	Both
carm1	IL8	Process	Both
carm1	p50	Association	Both
carm1	p50	Process	Both
carm1	RelA-p65	Association	Both
carm1	RelA-p65	Process	Both
carm1	S-adenosylhomocysteine	Process	Both
carm1	S-adenosylmethionine	Process	Both
carm1	SRC-1	Association	Both
carm1	SRC-1	Process	Both
Caspase-2	CRADD	Association	Both
Caspase-2	CRADD	Dissociation	Both
Caspase-2	proCaspase-2	Association	Both
Caspase-2	proCaspase-2	Dissociation	Both
Caspase-2	RIP	Association	Both
Caspase-2	RIP	Dissociation	Both
Caspase-2	TNF-alpha	Association	Both
Caspase-2	TNF-alpha	Dissociation	Both
Caspase-2	TNFR1	Association	Both
Caspase-2	TNFR1	Dissociation	Both

Caspase-2	TRADD	Association	Both
Caspase-2	TRADD	Dissociation	Both
Caspase-8	FADD	Association	Both
Caspase-8	FADD	Dissociation	Both
Caspase-8	proCaspase-3	Process	Both
Caspase-8	tBid	Dissociation	Both
Caspase-8	TNF-alpha	Association	Both
Caspase-8	TNF-alpha	Dissociation	Both
Caspase-8	TNFR1	Association	Both
Caspase-8	TNFR1	Dissociation	Both
Caspase-8	TRADD	Association	Both
Caspase-8	TRADD	Dissociation	Both
CBP	Cdk9	Association	Both
CBP	Cdk9	Process	Both
CBP	CoA	Process	Both
CBP	cyclinT1	Association	Both
CBP	cyclinT1	Process	Both
CBP	histone H3	Process	Both
CBP	IKK	Process	Both
CBP	IKK-alpha	Process	Both
CBP	IL8	Process	Both
CBP	p50	Association	Both
CBP	p50	Process	Both
CBP	RelA-p65	Association	Both
CBP	RelA-p65	Process	Both
CBP	S-adenosylhomocysteine	Process	Both
CBP	S-adenosylmethionine	Process	Both
CBP	SRC-1	Association	Both
CBP	SRC-1	Process	Both
CD14	IRAK-1	Association	Both
CD14	IRAK-1	Process	Both
CD14	Ibp	Association	Both
CD14	Ibp	Process	Both
CD14	LPS	Association	Both
CD14	LPS	Process	Both
CD14	MD-2	Association	Both
CD14	MD-2	Process	Both
CD14	MEKK1	Association	Both
CD14	MyD88	Association	Both
CD14	MyD88	Process	Both
CD14	SITPEC	Association	Both
CD14	tab2	Process	Both
CD14	TLR4	Association	Both
CD14	TLR4	Process	Both
CD14	traf6	Association	Both
CD14	traf6	Process	Both
Cdc34	Cul-1	Process	Both
Cdc34	IkappaB-alpha	Process	Both

Cdc34	p50	Process	Both
Cdc34	RelA-p65	Process	Both
Cdc34	Ubc5	Process	Both
Cdc34	ubiquitin	Process	Both
Cdk9	cyclinT1	Association	Both
Cdk9	cyclinT1	Process	Both
Cdk9	IL8	Process	Both
Cdk9	p50	Association	Both
Cdk9	p50	Process	Both
Cdk9	RelA-p65	Association	Both
Cdk9	RelA-p65	Process	Both
Cdk9	SRC-1	Association	Both
Cdk9	SRC-1	Process	Both
ceramide	N-SMase	Process	Both
ceramide	SM	Process	Both
c-Jun	JNK1	Process	Both
c-Jun	JNK2	Process	Both
c-Jun	MKK7	Process	Both
CoA	histone H3	Process	Both
CoA	p50	Process	Both
CoA	RelA-p65	Process	Both
CoA	SRC-1	Process	Both
CRADD	proCaspase-2	Association	Both
CRADD	proCaspase-2	Dissociation	Both
CRADD	RIP	Association	Both
CRADD	RIP	Dissociation	Both
CRADD	TNF-alpha	Association	Both
CRADD	TNF-alpha	Dissociation	Both
CRADD	TNFR1	Association	Both
CRADD	TNFR1	Dissociation	Both
CRADD	TRADD	Association	Both
CRADD	TRADD	Dissociation	Both
Cul-1	IkappaB-alpha	Association	Both
Cul-1	IkappaB-alpha	Process	Both
Cul-1	p105	Association	Both
Cul-1	p50	Association	Both
Cul-1	p50	Process	Both
Cul-1	RelA-p65	Association	Both
Cul-1	RelA-p65	Process	Both
Cul-1	Ubc5	Process	Both
Cul-1	Ubc5C	Process	Both
Cul-1	ubiquitin	Association	Both
Cul-1	ubiquitin	Process	Both
cyclinT1	IL8	Process	Both
cyclinT1	p50	Association	Both
cyclinT1	p50	Process	Both
cyclinT1	RelA-p65	Association	Both
cyclinT1	RelA-p65	Process	Both

cyclinT1	SRC-1	Association	Both
cyclinT1	SRC-1	Process	Both
Cytochrome C	tBid	Process	Both
E1	tab2	Process	Both
E1	traf6	Process	Both
E1	ubiquitin	Process	Both
EAC	IKK	Process	Both
EAC	IKK-gamma	Process	Both
EAC	RIP	Association	Both
EAC	RIP	Dissociation	Both
EAC	TNF-alpha	Association	Both
EAC	TNF-alpha	Dissociation	Both
EAC	TNFR1	Association	Both
EAC	TNFR1	Dissociation	Both
EAC	TRADD	Association	Both
EAC	TRADD	Dissociation	Both
EAC	TRAF2	Association	Both
EAC	TRAF2	Dissociation	Both
EAC	ubiquitin	Dissociation	Both
FADD	TNF-alpha	Association	Both
FADD	TNF-alpha	Dissociation	Both
FADD	TNFR1	Association	Both
FADD	TNFR1	Dissociation	Both
FADD	TRADD	Association	Both
FADD	TRADD	Dissociation	Both
FAN	N-SMase	Process	Both
FAN	RACK1	Association	Both
FAN	RACK1	Process	Both
FAN	SM	Process	Both
FAN	TNF-alpha	Association	Both
FAN	TNF-alpha	Process	Both
FAN	TNFR1	Association	Both
FAN	TNFR1	Process	Both
histone H3	p50	Process	Both
histone H3	RelA-p65	Process	Both
histone H3	S-adenosylhomocysteine	Process	Both
histone H3	S-adenosylmethionine	Process	Both
histone H3	SRC-1	Process	Both
ICAM1	miR-221/222/222ab/1928	Process	Both
ICAM1	p50	Process	Both
ICAM1	RelA-p65	Process	Both
IkappaB-alpha	IKK	Process	Both
IkappaB-alpha	IKK-alpha	Process	Both
IkappaB-alpha	IKK-beta	Process	Both
IkappaB-alpha	IKK-gamma	Process	Both
IkappaB-alpha	p50	Association	Both
IkappaB-alpha	p50	Dissociation	Both
IkappaB-alpha	p50	Process	Both

IkappaB-alpha	RelA-p65	Association	Both
IkappaB-alpha	RelA-p65	Dissociation	Both
IkappaB-alpha	RelA-p65	Process	Both
IkappaB-alpha	Ubc5	Process	Both
IkappaB-alpha	Ubc5C	Process	Both
IkappaB-alpha	ubiquitin	Process	Both
IKK	IKK-alpha	Association	Both
IKK	IKK-alpha	Dissociation	Both
IKK	IKK-alpha	Process	Both
IKK	IKK-beta	Association	Both
IKK	IKK-beta	Dissociation	Both
IKK	IKK-beta	Process	Both
IKK	IKK-gamma	Association	Both
IKK	IKK-gamma	Dissociation	Both
IKK	IKK-gamma	Process	Both
IKK	MEKK1	Process	Both
IKK	NIK	Association	Both
IKK	NIK	Dissociation	Both
IKK	NIK	Process	Both
IKK	p105	Process	Both
IKK	p50	Process	Both
IKK	p62	Association	Both
IKK	p62	Dissociation	Both
IKK	p62	Process	Both
IKK	PKCzeta	Association	Both
IKK	PKCzeta	Dissociation	Both
IKK	PKCzeta	Process	Both
IKK	RelA-p65	Process	Both
IKK	RIP	Association	Both
IKK	RIP	Dissociation	Both
IKK	RIP	Process	Both
IKK	SITPEC	Process	Both
IKK	TAB1	Process	Both
IKK	tab2	Association	Both
IKK	tab2	Dissociation	Both
IKK	tab2	Process	Both
IKK	tab3	Association	Both
IKK	tab3	Dissociation	Both
IKK	tab3	Process	Both
IKK	TAK1	Association	Both
IKK	TAK1	Dissociation	Both
IKK	TAK1	Process	Both
IKK	TNF-alpha	Association	Both
IKK	TNF-alpha	Dissociation	Both
IKK	TNF-alpha	Process	Both
IKK	TNFR1	Association	Both
IKK	TNFR1	Dissociation	Both
IKK	TNFR1	Process	Both

IKK	TRADD	Association	Both
IKK	TRADD	Dissociation	Both
IKK	TRADD	Process	Both
IKK	TRAF2	Association	Both
IKK	TRAF2	Dissociation	Both
IKK	TRAF2	Process	Both
IKK	traf6	Process	Both
IKK-alpha	IKK-beta	Association	Both
IKK-alpha	IKK-beta	Dissociation	Both
IKK-alpha	IKK-beta	Process	Both
IKK-alpha	IKK-gamma	Association	Both
IKK-alpha	IKK-gamma	Dissociation	Both
IKK-alpha	IKK-gamma	Process	Both
IKK-alpha	MEKK1	Process	Both
IKK-alpha	NIK	Association	Both
IKK-alpha	NIK	Dissociation	Both
IKK-alpha	NIK	Process	Both
IKK-alpha	p50	Process	Both
IKK-alpha	p62	Association	Both
IKK-alpha	p62	Dissociation	Both
IKK-alpha	p62	Process	Both
IKK-alpha	PKCzeta	Association	Both
IKK-alpha	PKCzeta	Dissociation	Both
IKK-alpha	PKCzeta	Process	Both
IKK-alpha	ReIA-p65	Process	Both
IKK-alpha	RIP	Association	Both
IKK-alpha	RIP	Dissociation	Both
IKK-alpha	RIP	Process	Both
IKK-alpha	SITPEC	Process	Both
IKK-alpha	TAB1	Process	Both
IKK-alpha	tab2	Association	Both
IKK-alpha	tab2	Dissociation	Both
IKK-alpha	tab2	Process	Both
IKK-alpha	tab3	Association	Both
IKK-alpha	tab3	Dissociation	Both
IKK-alpha	tab3	Process	Both
IKK-alpha	TAK1	Association	Both
IKK-alpha	TAK1	Dissociation	Both
IKK-alpha	TAK1	Process	Both
IKK-alpha	TNF-alpha	Association	Both
IKK-alpha	TNF-alpha	Dissociation	Both
IKK-alpha	TNF-alpha	Process	Both
IKK-alpha	TNFR1	Association	Both
IKK-alpha	TNFR1	Dissociation	Both
IKK-alpha	TNFR1	Process	Both
IKK-alpha	TRADD	Association	Both
IKK-alpha	TRADD	Dissociation	Both
IKK-alpha	TRADD	Process	Both

IKK-alpha	TRAF2	Association	Both
IKK-alpha	TRAF2	Dissociation	Both
IKK-alpha	TRAF2	Process	Both
IKK-alpha	traf6	Process	Both
IKK-beta	IKK-gamma	Association	Both
IKK-beta	IKK-gamma	Dissociation	Both
IKK-beta	IKK-gamma	Process	Both
IKK-beta	MEKK1	Process	Both
IKK-beta	NIK	Association	Both
IKK-beta	NIK	Dissociation	Both
IKK-beta	NIK	Process	Both
IKK-beta	p105	Process	Both
IKK-beta	p50	Process	Both
IKK-beta	p62	Association	Both
IKK-beta	p62	Dissociation	Both
IKK-beta	p62	Process	Both
IKK-beta	PKCzeta	Association	Both
IKK-beta	PKCzeta	Dissociation	Both
IKK-beta	PKCzeta	Process	Both
IKK-beta	RelA-p65	Process	Both
IKK-beta	RIP	Association	Both
IKK-beta	RIP	Dissociation	Both
IKK-beta	RIP	Process	Both
IKK-beta	SITPEC	Process	Both
IKK-beta	TAB1	Process	Both
IKK-beta	tab2	Association	Both
IKK-beta	tab2	Dissociation	Both
IKK-beta	tab2	Process	Both
IKK-beta	tab3	Association	Both
IKK-beta	tab3	Dissociation	Both
IKK-beta	tab3	Process	Both
IKK-beta	TAK1	Association	Both
IKK-beta	TAK1	Dissociation	Both
IKK-beta	TAK1	Process	Both
IKK-beta	TNF-alpha	Association	Both
IKK-beta	TNF-alpha	Dissociation	Both
IKK-beta	TNF-alpha	Process	Both
IKK-beta	TNFR1	Association	Both
IKK-beta	TNFR1	Dissociation	Both
IKK-beta	TNFR1	Process	Both
IKK-beta	TRADD	Association	Both
IKK-beta	TRADD	Dissociation	Both
IKK-beta	TRADD	Process	Both
IKK-beta	TRAF2	Association	Both
IKK-beta	TRAF2	Dissociation	Both
IKK-beta	TRAF2	Process	Both
IKK-beta	traf6	Process	Both
IKK-gamma	MEKK1	Process	Both

IKK-gamma	NIK	Association	Both
IKK-gamma	NIK	Dissociation	Both
IKK-gamma	NIK	Process	Both
IKK-gamma	p50	Process	Both
IKK-gamma	p62	Association	Both
IKK-gamma	p62	Dissociation	Both
IKK-gamma	p62	Process	Both
IKK-gamma	PKCzeta	Association	Both
IKK-gamma	PKCzeta	Dissociation	Both
IKK-gamma	PKCzeta	Process	Both
IKK-gamma	RelA-p65	Process	Both
IKK-gamma	RIP	Association	Both
IKK-gamma	RIP	Dissociation	Both
IKK-gamma	RIP	Process	Both
IKK-gamma	SITPEC	Process	Both
IKK-gamma	TAB1	Process	Both
IKK-gamma	tab2	Association	Both
IKK-gamma	tab2	Dissociation	Both
IKK-gamma	tab2	Process	Both
IKK-gamma	tab3	Association	Both
IKK-gamma	tab3	Dissociation	Both
IKK-gamma	tab3	Process	Both
IKK-gamma	TAK1	Association	Both
IKK-gamma	TAK1	Dissociation	Both
IKK-gamma	TAK1	Process	Both
IKK-gamma	TNF-alpha	Association	Both
IKK-gamma	TNF-alpha	Dissociation	Both
IKK-gamma	TNF-alpha	Process	Both
IKK-gamma	TNFR1	Association	Both
IKK-gamma	TNFR1	Dissociation	Both
IKK-gamma	TNFR1	Process	Both
IKK-gamma	TRADD	Association	Both
IKK-gamma	TRADD	Dissociation	Both
IKK-gamma	TRADD	Process	Both
IKK-gamma	TRAF2	Association	Both
IKK-gamma	TRAF2	Dissociation	Both
IKK-gamma	TRAF2	Process	Both
IKK-gamma	traf6	Process	Both
IL-10	IL-1RI	Process	Both
IL-10	IL-1RII	Process	Both
IL-1beta-p17	IL-1RA	Association	Both
IL-1beta-p17	IL-1RA	Process	Both
IL-1beta-p17	IL-1RAcP	Association	Both
IL-1beta-p17	IL-1RAcP	Process	Both
IL-1beta-p17	IL-1RI	Association	Both
IL-1beta-p17	IL-1RI	Process	Both
IL-1beta-p17	IL-1RII	Association	Both
IL-1beta-p17	IRAK-1	Association	Both

IL-1beta-p17	IRAK-1	Process	Both
IL-1beta-p17	IRAK-2	Association	Both
IL-1beta-p17	IRAK-2	Process	Both
IL-1beta-p17	IRAK-4	Association	Both
IL-1beta-p17	IRAK-4	Process	Both
IL-1beta-p17	MEKK1	Association	Both
IL-1beta-p17	MyD88	Association	Both
IL-1beta-p17	MyD88	Process	Both
IL-1beta-p17	Pellino1	Process	Both
IL-1beta-p17	SITPEC	Association	Both
IL-1beta-p17	tab2	Process	Both
IL-1beta-p17	traf6	Association	Both
IL-1beta-p17	traf6	Process	Both
IL-1RA	IL-1RAcP	Association	Both
IL-1RA	IL-1RAcP	Process	Both
IL-1RA	IL-1RI	Association	Both
IL-1RA	IL-1RI	Process	Both
IL-1RA	IL-1RII	Association	Both
IL-1RA	IRAK-1	Association	Both
IL-1RA	IRAK-1	Process	Both
IL-1RA	IRAK-2	Association	Both
IL-1RA	IRAK-2	Process	Both
IL-1RA	IRAK-4	Association	Both
IL-1RA	IRAK-4	Process	Both
IL-1RA	MEKK1	Association	Both
IL-1RA	MyD88	Association	Both
IL-1RA	MyD88	Process	Both
IL-1RA	Pellino1	Process	Both
IL-1RA	SITPEC	Association	Both
IL-1RA	tab2	Process	Both
IL-1RA	traf6	Association	Both
IL-1RA	traf6	Process	Both
IL-1RAcP	IL-1RI	Association	Both
IL-1RAcP	IL-1RI	Process	Both
IL-1RAcP	IL-1RII	Association	Both
IL-1RAcP	IRAK-1	Association	Both
IL-1RAcP	IRAK-1	Process	Both
IL-1RAcP	IRAK-2	Association	Both
IL-1RAcP	IRAK-2	Process	Both
IL-1RAcP	IRAK-4	Association	Both
IL-1RAcP	IRAK-4	Process	Both
IL-1RAcP	MEKK1	Association	Both
IL-1RAcP	MyD88	Association	Both
IL-1RAcP	MyD88	Process	Both
IL-1RAcP	Pellino1	Process	Both
IL-1RAcP	SITPEC	Association	Both
IL-1RAcP	tab2	Process	Both
IL-1RAcP	traf6	Association	Both

IL-1RAcP	traf6	Process	Both
IL-1RI	IL-1RII	Association	Both
IL-1RI	IL-1RII	Process	Both
IL-1RI	IRAK-1	Association	Both
IL-1RI	IRAK-1	Process	Both
IL-1RI	IRAK-2	Association	Both
IL-1RI	IRAK-2	Process	Both
IL-1RI	IRAK-4	Association	Both
IL-1RI	IRAK-4	Process	Both
IL-1RI	MEKK1	Association	Both
IL-1RI	MyD88	Association	Both
IL-1RI	MyD88	Process	Both
IL-1RI	Pellino1	Process	Both
IL-1RI	SITPEC	Association	Both
IL-1RI	tab2	Process	Both
IL-1RI	traf6	Association	Both
IL-1RI	traf6	Process	Both
IL8	p50	Process	Both
IL8	RelA-p65	Process	Both
IL8	SRC-1	Process	Both
importin-alpha3	p50	Association	Both
importin-alpha3	RelA-p65	Association	Both
IRAK-1	IRAK-2	Association	Both
IRAK-1	IRAK-2	Process	Both
IRAK-1	IRAK-4	Association	Both
IRAK-1	IRAK-4	Dissociation	Both
IRAK-1	IRAK-4	Process	Both
IRAK-1	Ibp	Association	Both
IRAK-1	Ibp	Process	Both
IRAK-1	LPS	Association	Both
IRAK-1	LPS	Process	Both
IRAK-1	MD-2	Association	Both
IRAK-1	MD-2	Process	Both
IRAK-1	MEKK1	Association	Both
IRAK-1	MyD88	Association	Both
IRAK-1	MyD88	Process	Both
IRAK-1	Pellino1	Dissociation	Both
IRAK-1	Pellino1	Process	Both
IRAK-1	SITPEC	Association	Both
IRAK-1	tab2	Dissociation	Both
IRAK-1	tab2	Process	Both
IRAK-1	TLR4	Association	Both
IRAK-1	TLR4	Process	Both
IRAK-1	traf6	Association	Both
IRAK-1	traf6	Dissociation	Both
IRAK-1	traf6	Process	Both
IRAK-2	IRAK-4	Association	Both
IRAK-2	IRAK-4	Process	Both

IRAK-2	MEKK1	Association	Both
IRAK-2	MyD88	Association	Both
IRAK-2	MyD88	Process	Both
IRAK-2	Pellino1	Process	Both
IRAK-2	SITPEC	Association	Both
IRAK-2	tab2	Process	Both
IRAK-2	traf6	Association	Both
IRAK-2	traf6	Process	Both
IRAK-4	MEKK1	Association	Both
IRAK-4	MyD88	Association	Both
IRAK-4	MyD88	Process	Both
IRAK-4	Pellino1	Dissociation	Both
IRAK-4	Pellino1	Process	Both
IRAK-4	SITPEC	Association	Both
IRAK-4	tab2	Dissociation	Both
IRAK-4	tab2	Process	Both
IRAK-4	traf6	Association	Both
IRAK-4	traf6	Dissociation	Both
IRAK-4	traf6	Process	Both
JNK1	MKK4	Process	Both
JNK1	MKK7	Association	Both
JNK1	MKK7	Process	Both
JNK1	TAB1	Process	Both
JNK2	MKK4	Process	Both
lbp	LPS	Association	Both
lbp	LPS	Process	Both
lbp	MD-2	Association	Both
lbp	MD-2	Process	Both
lbp	MEKK1	Association	Both
lbp	MyD88	Association	Both
lbp	MyD88	Process	Both
lbp	SITPEC	Association	Both
lbp	tab2	Process	Both
lbp	TLR4	Association	Both
lbp	TLR4	Process	Both
lbp	traf6	Association	Both
lbp	traf6	Process	Both
LPS	MD-2	Association	Both
LPS	MD-2	Process	Both
LPS	MEKK1	Association	Both
LPS	MyD88	Association	Both
LPS	MyD88	Process	Both
LPS	SITPEC	Association	Both
LPS	tab2	Process	Both
LPS	TLR4	Association	Both
LPS	TLR4	Process	Both
LPS	traf6	Association	Both
LPS	traf6	Process	Both

MD-2	MEKK1	Association	Both
MD-2	MyD88	Association	Both
MD-2	MyD88	Process	Both
MD-2	SITPEC	Association	Both
MD-2	tab2	Process	Both
MD-2	TLR4	Association	Both
MD-2	TLR4	Process	Both
MD-2	traf6	Association	Both
MD-2	traf6	Process	Both
MEKK1	MKK7	Process	Both
MEKK1	MyD88	Association	Both
MEKK1	SITPEC	Association	Both
MEKK1	SITPEC	Process	Both
MEKK1	TLR4	Association	Both
MEKK1	TNF-alpha	Association	Both
MEKK1	TNF-alpha	Process	Both
MEKK1	TNFR1	Association	Both
MEKK1	TNFR1	Process	Both
MEKK1	TRADD	Association	Both
MEKK1	TRADD	Process	Both
MEKK1	TRAF2	Association	Both
MEKK1	TRAF2	Process	Both
MEKK1	traf6	Association	Both
MEKK1	traf6	Process	Both
miR-126-3p	VCAM1	Process	Both
MKK4	MKK7	Process	Both
MKK4	TRAF2	Process	Both
MKK6	p38alpha	Process	Both
MKK6	TAB1	Process	Both
MKK6	tab2	Process	Both
MKK6	TAK1	Process	Both
MKK6	traf6	Process	Both
MKK7	p38alpha	Process	Both
MKK7	TNF-alpha	Process	Both
MKK7	TNFR1	Process	Both
MKK7	TRADD	Process	Both
MKK7	TRAF2	Process	Both
MSK1	p50	Process	Both
MSK1	RelA-p65	Process	Both
MyD88	Pellino1	Process	Both
MyD88	SITPEC	Association	Both
MyD88	ST2	Association	Both
MyD88	tab2	Process	Both
MyD88	TLR4	Association	Both
MyD88	TLR4	Process	Both
MyD88	TLR5	Process	Both
MyD88	traf6	Association	Both
MyD88	traf6	Process	Both

NFKBIA	p50	Process	Both
NFKBIA	RelA-p65	Process	Both
NIK	p62	Association	Both
NIK	p62	Dissociation	Both
NIK	p62	Process	Both
NIK	PKCzeta	Association	Both
NIK	PKCzeta	Dissociation	Both
NIK	PKCzeta	Process	Both
NIK	RIP	Association	Both
NIK	RIP	Dissociation	Both
NIK	RIP	Process	Both
NIK	TNF-alpha	Association	Both
NIK	TNF-alpha	Dissociation	Both
NIK	TNF-alpha	Process	Both
NIK	TNFR1	Association	Both
NIK	TNFR1	Dissociation	Both
NIK	TNFR1	Process	Both
NIK	TRADD	Association	Both
NIK	TRADD	Dissociation	Both
NIK	TRADD	Process	Both
NIK	TRAF2	Association	Both
NIK	TRAF2	Dissociation	Both
NIK	TRAF2	Process	Both
N-SMase	RACK1	Process	Both
N-SMase	SM	Process	Both
N-SMase	TNF-alpha	Process	Both
N-SMase	TNFR1	Process	Both
p105	p50	Dissociation	Both
p105	ubiquitin	Association	Both
p105	ubiquitin	Dissociation	Both
p38alpha	TAB1	Process	Both
p50	Pin1	Association	Both
p50	PKAc	Process	Both
p50	RelA-p65	Association	Both
p50	RelA-p65	Dissociation	Both
p50	RelA-p65	Process	Both
p50	S-adenosylhomocysteine	Process	Both
p50	S-adenosylmethionine	Process	Both
p50	SELE	Process	Both
p50	SOCS-1	Association	Both
p50	SOCS-1	Dissociation	Both
p50	SRC-1	Association	Both
p50	SRC-1	Process	Both
p50	TNFAIP3	Process	Both
p50	Ubc5	Association	Both
p50	Ubc5	Process	Both
p50	Ubc5A	Association	Both
p50	Ubc5C	Process	Both

p50	ubiquitin	Association	Both
p50	ubiquitin	Dissociation	Both
p50	ubiquitin	Process	Both
p50	VCAM1	Process	Both
p50	Wip1	Process	Both
p62	PKCzeta	Association	Both
p62	PKCzeta	Dissociation	Both
p62	PKCzeta	Process	Both
p62	RIP	Association	Both
p62	RIP	Dissociation	Both
p62	RIP	Process	Both
p62	TNF-alpha	Association	Both
p62	TNF-alpha	Dissociation	Both
p62	TNF-alpha	Process	Both
p62	TNFR1	Association	Both
p62	TNFR1	Dissociation	Both
p62	TNFR1	Process	Both
p62	TRADD	Association	Both
p62	TRADD	Dissociation	Both
p62	TRADD	Process	Both
p62	TRAF2	Association	Both
p62	TRAF2	Dissociation	Both
p62	TRAF2	Process	Both
Pellino1	tab2	Dissociation	Both
Pellino1	tab2	Process	Both
Pellino1	traf6	Dissociation	Both
Pellino1	traf6	Process	Both
Pin1	RelA-p65	Association	Both
PKAc	RelA-p65	Process	Both
PKCzeta	RIP	Association	Both
PKCzeta	RIP	Dissociation	Both
PKCzeta	RIP	Process	Both
PKCzeta	TNF-alpha	Association	Both
PKCzeta	TNF-alpha	Dissociation	Both
PKCzeta	TNF-alpha	Process	Both
PKCzeta	TNFR1	Association	Both
PKCzeta	TNFR1	Dissociation	Both
PKCzeta	TNFR1	Process	Both
PKCzeta	TRADD	Association	Both
PKCzeta	TRADD	Dissociation	Both
PKCzeta	TRADD	Process	Both
PKCzeta	TRAF2	Association	Both
PKCzeta	TRAF2	Dissociation	Both
PKCzeta	TRAF2	Process	Both
proCaspase-2	RIP	Association	Both
proCaspase-2	RIP	Dissociation	Both
proCaspase-2	TNF-alpha	Association	Both
proCaspase-2	TNF-alpha	Dissociation	Both

proCaspase-2	TNFR1	Association	Both
proCaspase-2	TNFR1	Dissociation	Both
proCaspase-2	TRADD	Association	Both
proCaspase-2	TRADD	Dissociation	Both
RACK1	SM	Process	Both
RACK1	TNF-alpha	Association	Both
RACK1	TNF-alpha	Process	Both
RACK1	TNFR1	Association	Both
RACK1	TNFR1	Process	Both
RelA-p65	S-adenosylhomocysteine	Process	Both
RelA-p65	S-adenosylmethionine	Process	Both
RelA-p65	SELE	Process	Both
RelA-p65	SOCS-1	Association	Both
RelA-p65	SOCS-1	Dissociation	Both
RelA-p65	SRC-1	Association	Both
RelA-p65	SRC-1	Process	Both
RelA-p65	TNFAIP3	Process	Both
RelA-p65	Ubc5	Association	Both
RelA-p65	Ubc5	Process	Both
RelA-p65	Ubc5A	Association	Both
RelA-p65	Ubc5C	Process	Both
RelA-p65	ubiquitin	Association	Both
RelA-p65	ubiquitin	Dissociation	Both
RelA-p65	ubiquitin	Process	Both
RelA-p65	VCAM1	Process	Both
RelA-p65	Wip1	Process	Both
RIP	tab2	Association	Both
RIP	tab2	Dissociation	Both
RIP	tab2	Process	Both
RIP	tab3	Association	Both
RIP	tab3	Dissociation	Both
RIP	tab3	Process	Both
RIP	TAK1	Association	Both
RIP	TAK1	Dissociation	Both
RIP	TAK1	Process	Both
RIP	TNF-alpha	Association	Both
RIP	TNF-alpha	Dissociation	Both
RIP	TNF-alpha	Process	Both
RIP	TNFR1	Association	Both
RIP	TNFR1	Dissociation	Both
RIP	TNFR1	Process	Both
RIP	TRADD	Association	Both
RIP	TRADD	Dissociation	Both
RIP	TRADD	Process	Both
RIP	TRAF2	Association	Both
RIP	TRAF2	Dissociation	Both
RIP	TRAF2	Process	Both
RIP	ubiquitin	Association	Both

RIP	ubiquitin	Dissociation	Both
S-adenosylhomocysteine	S-adenosylmethionine	Process	Both
S-adenosylhomocysteine	SRC-1	Process	Both
S-adenosylmethionine	SRC-1	Process	Both
SITPEC	TLR4	Association	Both
SITPEC	traf6	Association	Both
SITPEC	traf6	Process	Both
SM	TNF-alpha	Process	Both
SM	TNFR1	Process	Both
SOCS-1	Ubc5	Association	Both
SOCS-1	Ubc5A	Association	Both
SOCS-1	ubiquitin	Association	Both
SOCS-1	ubiquitin	Dissociation	Both
TAB1	tab2	Association	Both
TAB1	tab2	Process	Both
TAB1	TAK1	Association	Both
TAB1	TAK1	Process	Both
TAB1	traf6	Association	Both
TAB1	traf6	Process	Both
tab2	tab3	Association	Both
tab2	tab3	Dissociation	Both
tab2	tab3	Process	Both
tab2	TAK1	Association	Both
tab2	TAK1	Dissociation	Both
tab2	TAK1	Process	Both
tab2	TLR4	Process	Both
tab2	TRADD	Association	Both
tab2	TRADD	Dissociation	Both
tab2	TRADD	Process	Both
tab2	TRAF2	Association	Both
tab2	TRAF2	Dissociation	Both
tab2	TRAF2	Process	Both
tab2	traf6	Association	Both
tab2	traf6	Dissociation	Both
tab2	traf6	Process	Both
tab2	ubiquitin	Process	Both
tab3	TAK1	Association	Both
tab3	TAK1	Dissociation	Both
tab3	TAK1	Process	Both
tab3	TRADD	Association	Both
tab3	TRADD	Dissociation	Both
tab3	TRADD	Process	Both
tab3	TRAF2	Association	Both
tab3	TRAF2	Dissociation	Both
tab3	TRAF2	Process	Both
TAK1	TRADD	Association	Both
TAK1	TRADD	Dissociation	Both
TAK1	TRADD	Process	Both

TAK1	TRAF2	Association	Both
TAK1	TRAF2	Dissociation	Both
TAK1	TRAF2	Process	Both
TAK1	traf6	Association	Both
TAK1	traf6	Process	Both
TAK1	ubiquitin	Association	Both
TLR4	traf6	Association	Both
TLR4	traf6	Process	Both
TNF-alpha	TNFR1	Association	Both
TNF-alpha	TNFR1	Dissociation	Both
TNF-alpha	TNFR1	Process	Both
TNF-alpha	TRADD	Association	Both
TNF-alpha	TRADD	Dissociation	Both
TNF-alpha	TRADD	Process	Both
TNF-alpha	TRAF2	Association	Both
TNF-alpha	TRAF2	Dissociation	Both
TNF-alpha	TRAF2	Process	Both
TNF-alpha	ubiquitin	Association	Both
TNF-alpha	ubiquitin	Dissociation	Both
TNFR1	TRADD	Association	Both
TNFR1	TRADD	Dissociation	Both
TNFR1	TRADD	Process	Both
TNFR1	TRAF2	Association	Both
TNFR1	TRAF2	Dissociation	Both
TNFR1	TRAF2	Process	Both
TNFR1	ubiquitin	Association	Both
TNFR1	ubiquitin	Dissociation	Both
TRADD	TRAF2	Association	Both
TRADD	TRAF2	Dissociation	Both
TRADD	TRAF2	Process	Both
TRADD	ubiquitin	Association	Both
TRADD	ubiquitin	Dissociation	Both
TRAF2	ubiquitin	Association	Both
TRAF2	ubiquitin	Dissociation	Both
traf6	ubiquitin	Association	Both
traf6	ubiquitin	Process	Both
Ubc5	Ubc5A	Association	Both
Ubc5	Ubc5C	Process	Both
Ubc5	ubiquitin	Association	Both
Ubc5	ubiquitin	Process	Both
Ubc5A	ubiquitin	Association	Both

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ENSG00000069702		3.6	12	71893	0.90934
ENSG00000163513		3.6	12	71893	0.90934
ENSG00000017427		3.6	12	71893	0.90934
ENSG00000168036		3.6	12	71893	0.90934
ENSG00000164761		3.6	12	71893	0.90934
ENSG00000164136		3.6	12	71893	0.90934
ENSG00000118689		3.6	12	71893	0.90934
ENSG00000175387		3.6	12	71893	0.90934
ENSG00000108691		3.6	12	71893	0.90934
ENSG00000157404		3.6	12	71893	0.90934
ENSG00000160791		3.6	12	71893	0.90934
ENSG00000039068		3.6	12	71893	0.90934
ENSG00000112116		3.6	12	71893	0.90934
ENSG00000112115		3.6	12	71893	0.90934
ENSG00000090339		3.6	12	71893	0.90934
ENSG00000102245		3.6	12	71893	0.90934
ENSG00000173327		3.6	12	71893	0.90934
ENSG00000144381		3.6	12	71893	0.90934
ENSG00000168610		3.6	12	71893	0.90934
ENSG00000149968		3.6	12	71893	0.90934
ENSG00000006062		5.46	12	70106	0.74578536
ENSG00000106683		3.6	12	71893	0.90934
ENSG00000111321		5.46	12	70106	0.745759
ENSG00000226979		5.46	12	70106	0.745759
ENSG00000227507		5.46	12	70106	0.745759
ENSG00000115541		3.6	12	71893	0.90934
ENSG00000164305		3.6	12	71893	0.90934
ENSG00000113525		3.6	12	71893	0.90934
ENSG00000064012		3.6	12	71893	0.90934
ENSG00000072062		5.6	12	70973	0.807201
ENSG00000232810		3.6	12	71893	0.90934

ENSG00000067182		3.6	12	71893	0.90934
ENSG00000108094		6.12	12	70584	0.7465518
ENSG00000115457		6.75	12	70055	0.61936754
ENSG00000173039		6.75	12	70046	0.6259042
ENSG00000105810		6.75	12	70044	0.6250095
ENSG00000147162		6.75	12	70045	0.6155797
ENSG00000164088		6.75	12	70029	0.6124364
ENSG00000005381		5.3999996	12	71017	0.82925606
ENSG00000107968		6.6	12	70129	0.71335024
ENSG00000110330		5.5	12	70517	0.7119078
ENSG00000067900		6.75	12	70037	0.6123565
ENSG00000104365		6.75	12	70119	0.6526765
ENSG00000134058		6.75	12	70030	0.6123358
ENSG00000269335		5.75	12	70869	0.71404743
ENSG00000131788		5.76	12	70778	0.71407497
ENSG00000163702		6.75	12	70099	0.612196
ENSG00000177663		6.75	12	70099	0.612196
ENSG00000213341		6.75	12	70125	0.6153272
ENSG00000055208		6.75	12	70099	0.612196
ENSG00000056972		6.75	12	70099	0.612196
ENSG00000131323		7.035	12	65994	0.5407338
ENSG00000175104		6.75	12	70099	0.612196
ENSG00000162924		9.9	12	59326	0.46628165
ENSG00000135341		5.76	12	70043	0.6245046
ENSG00000129559		8.28	12	66741	0.54859954
ENSG00000173801		7.56	12	68114	0.59836376
ENSG00000105329		3.6	12	71893	0.90934
ENSG00000149591		7.6	12	68077	0.59836614
ENSG00000167749		7.6	12	68070	0.5983616
ENSG00000115170		7.5950003	12	68069	0.5983511
ENSG00000152484		7.6	12	68084	0.5983578
ENSG00000131653		6.8	12	69963	0.63348943
ENSG00000121989		7.5600004	12	68115	0.5983318
ENSG00000122641		7.5600004	12	68115	0.5983318
ENSG00000135503		7.5600004	12	68115	0.5983318
ENSG00000172349		7.6	12	68079	0.5983425
ENSG00000160633		7.6	12	68067	0.598348
ENSG00000141552		7.6	12	68076	0.598261
ENSG00000172840		7.5950003	12	68080	0.5983457
ENSG00000139567		7.5950003	12	68070	0.5983349
ENSG00000136807		7.5950003	12	68107	0.60283357
ENSG00000100234		7.5599995	12	68137	0.5983164
ENSG00000164850		3.6	12	71894	0.909338
ENSG00000112799		3.6	12	71894	0.909338
ENSG00000134061		3.6	12	71894	0.909338
ENSG00000169118		6.8499994	12	69866	0.63015866
ENSG00000115718		5.91	12	70681	0.71089166
ENSG00000178568		7.5950003	12	68082	0.5982364

ENSG00000065361		7.5950003	12	68082	0.59823585
ENSG00000141736		7.5950003	12	68082	0.5982351
ENSG00000104856		4.32	2	78	0.25144747
ENSG00000135960		5.76	12	69263	0.62076813
ENSG00000089041		6.6	12	70129	0.7012792
ENSG00000100079		6.6	12	70130	0.70127815
ENSG00000164951		7.5950003	12	68069	0.5983471
ENSG00000180772		5.91	12	70682	0.7108893
ENSG00000095739		6.6	12	70129	0.70127857
ENSG00000107014		6.6	12	70130	0.7012774
ENSG00000107779		7.5950003	12	68083	0.5980402
ENSG00000150093		9.585	12	60076	0.41584295
ENSG00000105647		7.9999995	12	66901	0.5182761
ENSG00000128342		6.6	12	70129	0.70127815
ENSG00000176797		6.6	12	70130	0.7012766
ENSG00000177243		6.6	12	70130	0.7012766
ENSG00000115687		6.75	12	70172	0.6347166
ENSG00000112425		6.75	12	70180	0.6347163
ENSG00000043093		9.27	12	63476	0.45494947
ENSG00000171855		6.6	12	70138	0.7012685
ENSG00000145675		7.9999995	12	66901	0.5182743
ENSG00000104814		7.5600004	12	65212	0.51734453
ENSG00000136279		7.5600004	12	65212	0.51734453
ENSG00000010671		9.599999	12	60063	0.4158373
ENSG00000101977		7.6	12	68110	0.59817326
ENSG00000108389		7.5950003	12	68134	0.59828806
ENSG00000157450		9.38	12	62732	0.45513147
ENSG00000204209		7.5599995	12	68194	0.5978195
ENSG00000100393		8	12	67011	0.5181211
ENSG00000110958		9.599999	12	60057	0.41586527
ENSG00000126351		9.599999	12	60093	0.41587228
ENSG00000174775		9.57	12	60167	0.41561633
ENSG00000100983		9.599999	12	60601	0.41573972
ENSG00000180370		7.5950003	12	68408	0.59760123
ENSG00000118503		3.6	12	71893	0.90934
ENSG00000197081		9	12	63755	0.42712894
ENSG00000131196		7.95	12	67021	0.517943
ENSG00000169194		3.6	12	71893	0.90934
ENSG00000113520		3.6	12	71893	0.90934
ENSG00000068903		7.8	12	67853	0.554528
ENSG00000147099		7.95	12	67030	0.5179252
ENSG00000150782		3.6	12	71893	0.90934
ENSG00000159110		9	12	63761	0.42710644
ENSG00000007171		3.6	12	71893	0.90934
ENSG00000048052		7.95	12	67033	0.51792264
ENSG00000115594		3.6	12	71893	0.90934
ENSG00000185338		6.91	12	69124	0.6298157
ENSG00000082146		9.595	12	60290	0.41571394

ENSG00000061273		7.95	12	67065	0.51789963
ENSG00000094631		7.95	12	67032	0.51791775
ENSG00000108840		7.95	12	67030	0.5179232
ENSG00000156711		7.5950003	12	68171	0.59766006
ENSG00000117399		9.599999	12	60352	0.41544947
ENSG00000188130		7.5950003	12	68166	0.59763104
ENSG00000108443		9.585	12	61285	0.41531238
ENSG00000117984		7.95	12	67071	0.51790935
ENSG00000213281		9.57	12	60140	0.4156918
ENSG00000185104		5.76	12	70777	0.7104392
ENSG00000129422		9	12	63755	0.4271303
ENSG00000263528		7.75	12	68025	0.5711993
ENSG00000177606		9.285	10	49709	0.32360092
ENSG00000198900		9.285	10	49709	0.32360092
ENSG00000137834		5.76	12	70777	0.710434
ENSG00000111653		6.91	12	69105	0.62207466
ENSG00000011275		8.91	12	59454	0.34724462
ENSG00000171206		9.495	12	60595	0.43240014
ENSG00000187391		5.76	12	70784	0.7104409
ENSG00000144802		7.92	12	67218	0.51772976
ENSG00000176697		5.76	12	70777	0.7104282
ENSG00000138794		5.76	12	70777	0.7104279
ENSG00000106624		5.76	12	70785	0.7104448
ENSG00000104408		9	12	63838	0.42702994
ENSG00000131080		8.85	12	65024	0.43020087
ENSG00000129988		5.76	12	70790	0.71043706
ENSG00000157227		5.76	12	70777	0.71042585
ENSG00000049130		7.92	12	67218	0.5177293
ENSG00000173163		8.610001	12	59328	0.3733167
ENSG00000177426		7.92	12	67220	0.5177254
ENSG00000100380		8.969999	12	63859	0.42679292
ENSG00000153233		5.76	12	70777	0.7104353
ENSG00000141753		7.92	12	67218	0.5177292
ENSG00000082074		9.599999	12	60086	0.41582003
ENSG00000275302		7.92	12	67218	0.5177297
ENSG00000126583		9	12	63769	0.42712083
ENSG00000154229		9	12	63769	0.42712083
ENSG00000166501		9	12	63769	0.42712083
ENSG00000095015		8.85	12	65059	0.43016466
ENSG00000130159		8.85	12	65059	0.43016466
ENSG00000213658		9.599999	12	60116	0.41576496
ENSG00000150630		8.969999	12	63866	0.42678547
ENSG00000106615		9.57	12	60071	0.4158295
ENSG00000225950		5.76	12	70777	0.71043473
ENSG00000146678		5.76	12	70777	0.710435
ENSG00000271503		7.92	12	67218	0.5177286
ENSG00000075213		7.92	12	67218	0.51772624
ENSG00000157933		7.92	12	67218	0.5177291

ENSG00000183691		5.76	12	70778	0.71040905
ENSG00000043462		9.599999	12	60148	0.41575575
ENSG00000051523		8.985001	12	63770	0.4270362
ENSG00000100365		8.985001	12	63770	0.4270362
ENSG00000116701		8.985001	12	63770	0.4270362
ENSG00000136238		8.985001	12	63770	0.4270362
ENSG00000142765		8.985001	12	63770	0.4270362
ENSG00000158517		8.985001	12	63770	0.4270362
ENSG00000165168		8.985001	12	63770	0.4270362
ENSG00000113721		5.76	12	70778	0.71040905
ENSG00000197635		7.92	12	67222	0.517722
ENSG00000134853		5.76	12	70778	0.7104186
ENSG00000121653		7.92	12	67218	0.5177258
ENSG00000102524		8.91	11	37216	0.2654545
ENSG00000213928		7.92	12	67219	0.5177216
ENSG00000121879		7.92	12	67220	0.5177101
ENSG00000078369		7.98	9	31781	0.24260649
ENSG00000115461		7.92	12	67218	0.5177259
ENSG00000185499		7.92	12	67218	0.5177259
ENSG00000170581		7.92	12	67219	0.517722
ENSG00000142166		7.92	12	67219	0.51772016
ENSG00000158813		7.92	12	63549	0.4400373
ENSG00000079385		8.969999	12	63900	0.42671067
ENSG00000187098		8.969999	12	63908	0.4267764
ENSG00000129315		7.92	12	67222	0.51771617
ENSG00000196083		7.92	12	67221	0.5176931
ENSG00000099942		10	12	57637	0.335366
ENSG00000107263		10	12	57637	0.335366
ENSG00000187266		10	12	57637	0.335366
ENSG00000124762		7.92	12	67219	0.5177215
ENSG00000277632		7.92	12	67219	0.51770365
ENSG00000120868		10	12	57686	0.33529928
ENSG00000132906		10	12	57686	0.33529928
ENSG00000172115		10	12	57686	0.33529928
ENSG00000154310		7.92	12	67220	0.51771235
ENSG00000131089		7.92	12	67236	0.5176874
ENSG00000102547		9.835001	10	34919	0.24541828
ENSG00000118046		9.835001	10	34919	0.24541828
ENSG00000135932		9.835001	10	34919	0.24541828
ENSG00000266173		9.835001	10	34919	0.24541828
ENSG00000140299		7.92	12	67235	0.5176878
ENSG00000197461		7.92	12	67233	0.5176887
ENSG00000127948		9.795	10	43756	0.24303655
ENSG00000109320		7.695	9	42750	0.24338467
ENSG00000088387		7.92	12	67237	0.5176855
ENSG00000085276		7.92	12	67218	0.517708
ENSG00000180228		7.92	12	67232	0.51767194
ENSG00000017797		7.92	12	67239	0.51766765

ENSG00000105974		8.969999	12	63876	0.4267289
ENSG00000140575		7.92	12	67222	0.51771337
ENSG00000171560		9.889999	10	43781	0.24304931
ENSG00000166949		9	12	63756	0.42712975
ENSG00000070831		7.92	12	67220	0.5176907
ENSG00000158092		7.92	12	67219	0.51770896
ENSG00000168067		7.995	9	31776	0.24262741
ENSG00000002330		9.93	10	43578	0.24308331
ENSG00000111276		7.9749994	9	31837	0.24258348
ENSG00000123374		7.9749994	9	31837	0.24258348
ENSG00000105141		9.9	12	59349	0.33481878
ENSG00000196642		8.91	12	64087	0.42654973
ENSG00000163935		9.9	12	59330	0.33482593
ENSG00000157625		7.92	12	64880	0.44248962
ENSG00000178522		9.9	12	59330	0.33482286
ENSG00000204628		9	12	63756	0.4271173
ENSG00000088832		8.969999	12	63860	0.42677236
ENSG00000108622		9.889999	10	43734	0.24306636
ENSG00000137802		9.9	12	59330	0.33482626
ENSG00000111802		9.225	12	55447	0.33578593
ENSG00000171522		9.9	12	59330	0.33482534
ENSG00000067082		8.91	12	64088	0.42654967
ENSG00000162733		8.91	12	64102	0.42653918
ENSG00000110651		9.9	12	59332	0.33482435
ENSG00000109458		8.969999	12	63910	0.42671496
ENSG00000019991		9.9	12	59334	0.33482125
ENSG00000127914		9.9	12	59335	0.3348233
ENSG00000091879		9.91	10	43975	0.24301484
ENSG00000103056		9.9	12	59336	0.33482343
ENSG00000132024		9.9	12	59333	0.3348239
ENSG00000138668		8.91	12	59459	0.35119116
ENSG00000103490		9.9	12	59334	0.33482435
ENSG00000264522		8.61	12	59380	0.36004668
ENSG00000141867		9.455	10	48628	0.25022906
ENSG00000143437		9.780001	10	43703	0.24304433
ENSG00000020426		9.38	10	48880	0.2501911
ENSG00000134480		9.38	10	48880	0.2501911
ENSG00000184990		9.9	12	59367	0.33481124

FDR	Z-Score	Ranks sum
0.00	25.515682	2
0.00	25.515682	4
0.00	25.24933	10
0.00	25.109789	16
0.00	25.109789	16
0.00	25.109789	16
0.00	25.109789	20
0.00	25.109789	22
0.00	25.109789	22
0.00	25.109789	24
0.00	23.785404	32
0.00	23.785404	32
0.00	23.785404	32
0.00	23.785404	32
0.00	23.785404	34
0.00	17.603453	51
0.00	17.603453	53
0.00	17.603453	55
0.00	17.603453	55
0.00	17.347782	58
0.00	17.347782	60
0.00	17.347782	62
0.00	16.325098	68
0.00	15.6443615	71
0.00	15.395652	79
0.00	15.6443615	81
0.00	14.8982315	84
0.00	14.649521	86
0.00	14.649521	88
0.00	14.649521	92
0.00	14.649521	94
0.00	12.908551	102
0.00	12.908551	104
0.00	12.411131	108
0.00	9.924029	114
0.00	9.177899	123
0.00	8.92919	126
0.00	9.177899	126
0.00	8.680479	132
0.00	8.92919	134
0.00	8.444952	137
0.00	8.444952	139
0.00	8.444952	139
0.00	8.444952	139
0.00	8.444952	139
0.00	8.444952	141

0.00	8.444952	141
0.00	8.444952	141
0.00	8.444952	141
0.00	7.4784894	157
0.00	7.4784894	161
0.00	7.4784894	165
0.00	7.4784894	165
0.00	7.4784894	165
0.00	7.4784894	165
0.00	7.4784894	165
0.00	6.7536426	174
0.00	6.7536426	180
0.00	6.7536426	182
0.00	5.862493	190
0.00	5.862493	192
0.00	5.393531	196
0.00	5.393531	198
0.00	5.393531	200
0.00	5.393531	200
0.00	5.393531	202
0.00	5.393531	204
0.00	5.1354814	208
0.00	5.1354814	210
0.00	3.9684856	214
0.00	3.7350864	216
0.00	3.7350864	218
0.00	3.7350864	220
0.00	3.7350864	224
0.00	3.7350864	226
0.00	3.7350864	230
0.00	3.4077682	233
0.00	3.1813836	239
0.00	3.1813836	243
0.00	3.1813836	245
0.00	2.5022295	269
0.00	2.5022295	271
0.00	2.4914422	275
0.00	3.4883113	277
0.00	2.4914422	279
0.00	3.3829823	281
0.00	3.3829823	281
0.00	3.3829823	281
0.00	2.4806724	283
0.00	2.4806724	283
0.00	2.2562785	288
0.00	2.2562785	292
0.00	2.7416925	292
0.00	2.2562785	296

0.00	2.031885	322
0.01	2.1583393	326
0.01	2.8468504	338
0.02	2.6685882	339
0.03	2.542868	345
0.01	2.6078267	348
0.01	2.5822856	351
0.01	1.8166571	352
0.00	1.8473707	358
0.02	1.8184592	361
0.04	2.451285	364
0.02	2.1128314	366
0.04	2.346676	366
0.03	1.6740329	384
0.04	1.6588471	391
0.05	2.0695095	393
0.05	2.0695095	393
0.04	2.021259	394
0.05	2.0686812	394
0.05	2.069004	395
0.01	2.5663161	396
0.05	2.0683603	398
0.00	6.650155	402
0.04	1.7717301	406
0.03	2.1377385	423
0.00	1.7430931	428
0.00	1.3587039	429
0.01	1.7195715	432
0.00	1.731232	433
0.01	1.6844014	439
0.01	1.6811485	442
0.05	1.5657457	445
0.01	1.693381	445
0.01	1.693381	445
0.01	1.693381	445
0.01	1.681531	446
0.01	1.6682975	449
0.01	1.6981487	449
0.01	1.6640131	454
0.01	1.6671054	455
0.01	1.6284322	457
0.01	1.6641697	459
0.00	1.2649971	460
0.00	1.2615731	462
0.00	1.2615731	462
0.02	1.424171	465
0.04	1.2780058	471
0.01	1.6562477	471

0.01	1.6563139	471
0.01	1.6563655	471
0.00	9.694386	474
0.00	1.4052681	476
0.00	1.3085307	477
0.00	1.3114457	478
0.01	1.5548629	479
0.04	1.2524608	481
0.00	1.3057415	481
0.00	1.308338	482
0.01	1.5984213	482
0.01	2.849528	482
0.03	1.6607733	483
0.00	1.3043623	484
0.00	1.3081578	484
0.00	1.3081578	484
0.03	1.3217078	484
0.03	1.3190727	486
0.01	2.119744	486
0.00	1.3028532	488
0.03	1.6557599	491
0.04	2.010294	494
0.04	2.010294	494
0.01	2.618889	495
0.02	1.5310167	496
0.02	1.4546616	499
0.02	1.8615283	504
0.02	1.4358637	510
0.05	1.5372753	511
0.01	2.2056735	516
0.01	2.1791701	517
0.02	2.4829588	517
0.01	2.2672687	518
0.02	1.4013838	522
0.00	1.1343101	528
0.01	1.8112867	528
0.02	1.4142506	529
0.00	1.1343101	530
0.00	1.1343101	532
0.02	1.3698407	532
0.02	1.3974826	534
0.00	1.1343101	535
0.01	1.7704278	535
0.00	1.1343101	537
0.02	1.3973957	537
0.00	1.1343101	539
0.03	1.2146442	539
0.01	2.0868638	539

0.03	1.3862103	541
0.03	1.3618859	546
0.03	1.3528996	547
0.03	1.285942	549
0.01	1.9345831	556
0.04	1.2603947	559
0.02	1.9173793	559
0.03	1.2937016	565
0.01	1.7966001	566
0.03	1.0897201	570
0.01	1.5686253	570
0.04	1.2332013	574
0.01	2.2259452	576
0.01	2.2259452	576
0.02	1.0866207	579
0.03	1.1652129	579
0.02	1.7870173	581
0.01	1.4411689	582
0.03	1.0605493	583
0.02	1.2481622	583
0.03	1.0690925	586
0.03	1.0713297	586
0.05	1.0506582	588
0.02	1.5188372	590
0.02	1.4212871	591
0.02	1.0498791	593
0.03	1.0598683	594
0.03	1.2322732	594
0.01	1.6696557	594
0.02	1.245107	595
0.03	1.4982194	595
0.04	1.0350901	598
0.03	1.2259469	598
0.01	1.5812954	598
0.03	1.2243251	599
0.01	1.4074908	599
0.01	1.4074908	599
0.01	1.4074908	599
0.04	1.3734448	602
0.04	1.3734448	602
0.01	1.5740044	602
0.03	1.4386523	603
0.01	1.5662229	603
0.04	1.0128971	606
0.03	1.0027324	609
0.04	1.2171644	609
0.04	1.2180241	609
0.04	1.2151346	610

0.05	1.0179756	611
0.01	1.5598011	611
0.02	1.3809861	612
0.02	1.3809861	612
0.02	1.3809861	612
0.02	1.3809861	612
0.02	1.3809861	612
0.02	1.3809861	612
0.02	1.3809861	612
0.04	1.0032418	614
0.03	1.2208937	614
0.05	1.0005448	616
0.03	1.2096031	618
0.01	1.7353129	620
0.03	1.2152371	621
0.03	1.2247334	621
0.02	1.9368281	622
0.04	1.200358	623
0.04	1.2001833	623
0.03	1.2059002	625
0.03	1.2098798	626
0.01	1.2597772	628
0.05	1.3360722	632
0.03	1.3022013	638
0.04	1.1955749	641
0.04	1.1984386	649
0.04	1.4703811	650
0.04	1.4703811	650
0.04	1.4703811	650
0.05	1.1724962	652
0.04	1.1933305	652
0.05	1.5147556	652
0.05	1.5147556	652
0.05	1.5147556	652
0.04	1.175839	655
0.05	1.1959542	657
0.03	1.6348159	657
0.03	1.6348159	657
0.03	1.6348159	657
0.03	1.6348159	657
0.05	1.1950666	658
0.04	1.192116	659
0.02	1.6571015	660
0.01	1.5972216	662
0.05	1.1904196	663
0.05	1.1685082	665
0.05	1.1877697	666
0.05	1.1836513	669

0.05	1.2320014	669
0.03	1.1524434	671
0.03	1.5700408	671
0.01	1.1992165	676
0.05	1.1606978	678
0.04	1.0892324	691
0.02	1.4689363	694
0.02	1.3219874	712
0.02	1.3293632	722
0.02	1.3293632	722
0.04	1.2508427	723
0.05	1.1622107	724
0.04	1.2230949	729
0.03	1.0469893	736
0.05	1.2187074	740
0.02	1.0624357	741
0.04	1.0888858	741
0.02	1.2505156	741
0.04	1.2007021	743
0.02	1.17512	750
0.05	1.1962769	751
0.05	1.065588	756
0.04	1.0592271	763
0.05	1.1714522	769
0.05	1.026577	770
0.05	1.1727505	774
0.05	1.1691952	775
0.05	1.1873254	793
0.03	1.1287276	796
0.04	1.1056803	797
0.04	1.0414926	800
0.04	1.0793577	805
0.02	1.0028156	808
0.04	1.0719167	822
0.03	1.1202061	823
0.04	1.0640048	829
0.04	1.0640048	829
0.04	1.0061295	840

Table S4: IBD target genes, with source of data

ID	IBD importance	IBD Causal	IBD Correlative	IBD Mechanism	IBD Negative
TNF	10	+	+		+
TNFRSF11B	10	+	+		+
TNFRSF18	10	+	+		+
TNFRSF1A	10	+	+		+
TNFRSF4	10	+	+		+
TNFRSF6B	10	+	+		+
TNFRSF9	10	+	+		+
TNFSF11	10	+	+		+
TNFSF14	10	+	+		+
TNFSF15	10	+	+		+
TNFSF18	10	+	+		+
TNFSF4	10	+	+		+
IL10	10	+	+	+	+
IL13	10	+	+	+	+
IL15	10	+	+	+	+
IL15RA	10	+	+	+	+
IL17A	10	+	+	+	+
IL17F	10	+	+	+	+
IL18	10	+	+	+	+
IL18RAP	10	+	+	+	+
IL1A	10	+	+	+	+
IL1B	10	+	+	+	+
IL1R1	10	+	+	+	+
IL1RN	10	+	+	+	+
IL21	10	+	+	+	+
IL22	10	+	+	+	+
IL23R	10	+	+	+	+
IL25	10	+	+	+	+
IL26	10	+	+	+	+
IL27	10	+	+	+	+
IL31RA	10	+	+	+	+
IL4	10	+	+	+	+
IL5	10	+	+	+	+
IL6	10	+	+	+	+
IL6ST	10	+	+	+	+
CCL11	8	+	+	+	+
CCL13	8	+	+	+	+
CCL17	8	+	+	+	+
CCL2	8	+	+	+	+
CCL20	8	+	+	+	+
CCL26	8	+	+	+	+
CCR5	8	+	+	+	+

CCR6	8	+	+	+	+
CX3CL1	8	+	+	+	+
CXCL16	8	+	+	+	+
CXCL6	8	+	+	+	+
CXCL8	8	+	+	+	+
CXCR5	8	+	+	+	+
MAP3K8	5	+	+		
MAPK1	5	+	+		
MAPK3	5	+	+		
MAPK8	5	+	+		
SELP	5	+	+		
SELPLG	5	+	+		
STAT1	5	+	+		
STAT3	5	+	+		
STAT4	5	+	+		
STAT6	5	+	+		
IFNAR1	4	+	+		
IFNG	4	+	+		
IFNGR2	4	+	+		
NOD1	4	+	+		
NOD2	4	+	+		
VEGFA	4	+	+		
HSPA6	3	+	+		
HSPD1	3	+	+		
ICAM1	3	+	+		
IL12A	3	+	+		
IL12B	3	+	+		
MMP1	3	+	+		
MMP10	3	+	+		
MMP2	3	+	+		
MMP3	3	+	+		
MMP7	3	+	+		
MMP9	3	+	+		
TGFB1	3	+	+		
TLR2	3	+	+		
TLR3	3	+	+		
TLR4	3	+	+		
ADAM15	3		+		
ADAM30	3		+		
ALPI	3				
BMP7	3	+		+	
EPO	3				
CSF2	2	+		+	
CTNNB1	2		+		

DUSP1	2				
DUSP22	2				
FASLG	2				
GPX2	2	+	+		
GPX4	2	+	+		
IGF1	2	+	+		
IGSF6	2	+	+		
IL2	2	+	+		
IL2RA	2	+	+		
KIT	2	+	+		
MPO	2	+	+		
NFKB2	2	+	+		
NOS2	2	+	+		
PRKCB	2	+	+		
PTK2B	2	+	+		
PTPN22	2	+	+		
REL	2	+	+		
RELA	2	+	+		
SELE	2	+	+		
SELL	2	+	+		
SMAD3	2	+	+		
TAB1	2	+	+		
TPMT	2	+	+		
ADCY3	1				
ALDH2	1				
CREB5	1				
CTSZ	1				
DAP	1				
DNMT3B	1				
EPHX2	1				
F2	1				+
ABCB1	1		+		
AOX1	1		+		
CASP8	1		+		
CDH1	1		+		
CPB2	1		+		
FGF7	1	+			
GALC	1	+			
GPR18	1	+			
GPR183	1	+			
GPR35	1	+			
GPR65	1	+			
HCK	1	+			
IPMK	1	+			

IRGM	1	+			
ITPA	1	+			
JAK2	1	+			
KCNN3	1	+			
KIF21B	1	+			
LACC1	1	+			
MST1	1	+			
NDUFA13	1	+			
PAK1	1	+			
PFKFB4	1	+			
PHACTR2	1	+			
PLA2G4A	1	+			
PLA2R1	1	+			
PMM1	1	+			
PRKAB1	1	+			
PTGER4	1	+			
PTGES	1	+			
PTGS2	1	+			
PTH	1	+			
PTPRC	1	+			
RASGRP1	1	+			
RPS6KA2	1	+			
RPS6KB1	1	+			
S1PR2	1	+			
TBXAS1	1	+			
TST	1	+			
TUBD1	1	+			
TYK2	1	+			
VDR	1	+			

IBD Preventative	IBD Prognosis	IBD Target	IBD GWAS prognosis	IBD GWAS susceptablity
+	+	+	+	+
+	+	+	+	+
+	+	+	+	+
+	+	+	+	+
+	+	+	+	+
+	+	+	+	+
+	+	+	+	+
+	+	+	+	+
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Table S5: List of IBD key-nodes, potential therapeutic targets for IBD

ID	Gene symbol	Score	FDR	Z-Score	Ranks sum
ENSG00000111537	*IFNG*	0.90934	0	25.515682	2
ENSG00000148344	*PTGES*	0.90934	0	25.109789	20
ENSG00000109471	*IL2*	0.90934	0	25.109789	24
ENSG00000174175	*SELP*	0.90934	0	23.785404	34
ENSG00000137462	*TLR2*	0.90934	0	17.603453	51
ENSG00000136869	*TLR4*	0.90934	0	17.603453	53
ENSG00000006210	*CX3CL1*	0.90934	0	25.109789	62
ENSG00000130427	*EPO*	0.90934	0	16.325098	68
ENSG00000026508	*CD44*	0.90934	0	15.644362	73
ENSG00000136689	*IL1RN*	0.90934	0	15.893072	79
ENSG00000169429	*CXCL8*	0.90934	0	14.898232	84
ENSG00000115009	*CCL20*	0.90934	0	14.649521	88
ENSG00000115353	*TACR1*	0.90934	0	14.649521	92
ENSG00000113302	*IL12B*	0.90934	0	14.649521	94
ENSG00000125538	*IL1B*	0.90934	0	9.924029	126
ENSG00000100985	*MMP9*	0.90934	0	8.680479	132
ENSG00000149269	*PAK1*	0.90934	0	8.444952	143
ENSG00000166888	*STAT6*	0.90934	0	25.515682	153
ENSG00000136244	*IL6*	0.90934	0	9.177899	155
ENSG00000164400	*CSF2*	0.90934	0	6.7536426	174
ENSG00000115008	*IL1A*	0.90934	0	6.7536426	180
ENSG00000113580	*NR3C1*	0.90934	0	19.889582	192
ENSG00000017427	*IGF1*	0.90934	0	6.512027	202
ENSG00000112715	*VEGFA*	0.90934	0	14.649521	206
ENSG00000164761	*TNFRSF11B*	0.90934	0	12.16242	208
ENSG00000164136	*IL15*	0.90934	0	5.1354814	210
ENSG00000118689	*FOXO3*	0.90934	0	8.444952	214
ENSG00000175387	*SMAD2*	0.90934	0	10.42145	216
ENSG00000108691	*CCL2*	0.90934	0	13.903391	218
ENSG00000160791	*CCR5*	0.90934	0	22.46102	224
ENSG00000039068	*CDH1*	0.90934	0	3.7350864	226
ENSG00000112115	*IL17A*	0.90934	0	9.924029	233
ENSG00000137752	*CASP1*	0.90934	0	3.4077682	235
ENSG00000090339	*ICAM1*	0.90934	0	3.1813836	239
ENSG00000102245	*CD40LG*	0.90934	0	3.1813836	243
ENSG00000100030	*MAPK1*	0.90934	0	17.347782	251
ENSG00000102882	*MAPK3*	0.90934	0	24.315157	260
ENSG00000144381	*HSPD1*	0.90934	0	2.5022295	269
ENSG00000115415	*STAT1*	0.90934	0	25.515682	273
ENSG00000149968	*MMP3*	0.90934	0	2.4914422	275
ENSG00000136634	*IL10*	0.90934	0	2.4914422	277

ENSG00000113525	*IL5*	0.90934	0	2.2562785	288
ENSG00000168036	*CTNNB1*	0.90934	0	25.515682	294
ENSG00000232810	*TNF*	0.90934	0	2.2562785	296
ENSG00000064012	*CASP8*	0.90934	0	24.050282	300
ENSG00000067182	*TNFRSF1A*	0.90934	0	2.031885	322
ENSG00000087245	*MMP2*	0.90934	0	8.92919	324
ENSG00000138378	*STAT4*	0.90934	0	5.862493	326
ENSG00000108094	*CUL2*	0.7465518	0.01	2.1583393	330
ENSG00000005381	*MPO*	0.8292561	0.01	1.8166571	354
ENSG00000105329	*TGFB1*	0.90934	0	3.1813836	429
ENSG00000168610	*STAT3*	0.90934	0	13.903391	458
ENSG00000107643	*MAPK8*	0.90934	0	19.889582	460
ENSG00000164850	*GPER1*	0.909338	0	1.2649971	460
ENSG00000118503	*TNFAIP3*	0.90934	0	1.1343101	528
ENSG00000169194	*IL13*	0.90934	0	5.862493	530
ENSG00000113520	*IL4*	0.90934	0	8.203337	532
ENSG00000150782	*IL18*	0.90934	0	3.7350864	535
ENSG00000007171	*NOS2*	0.90934	0	1.1343101	537
ENSG00000115594	*IL1R1*	0.90934	0	2.2562785	539
ENSG00000142208	*AKT1*	0.90934	0	15.644362	541
ENSG00000157404	*KIT*	0.90934	0.04	6.7536426	573

Table S6: IBD key-nodes and their associated PASS activities

Gene symbol	ID	Maximal radius	Score	Z-Score	FDR	Ranks sum
IFNG	ENSG00000111537	3.6	0.90934	25.515682	0	2
PTGES	ENSG00000148344	3.6	0.90934	25.109789	0	20
IL2	ENSG00000109471	3.6	0.90934	25.109789	0	24
SELP	ENSG00000174175	3.6	0.90934	23.785404	0	34
TLR2	ENSG00000137462	3.6	0.90934	17.603453	0	51
TLR4	ENSG00000136869	3.6	0.90934	17.603453	0	53
CD44	ENSG00000026508	3.6	0.90934	15.6443615	0	73
CXCL8	ENSG00000169429	3.6	0.90934	14.8982315	0	84
IL12B	ENSG00000113302	3.6	0.90934	14.649521	0	94
IL1B	ENSG00000125538	3.6	0.90934	9.924029	0	126
MMP9	ENSG00000100985	3.6	0.90934	8.680479	0	132
PAK1	ENSG00000149269	3.6	0.90934	8.444952	0	143
STAT6	ENSG00000166888	3.6	0.90934	25.515682	0	153
IL6	ENSG00000136244	3.6	0.90934	9.177899	0	155
CSF2	ENSG00000164400	3.6	0.90934	6.7536426	0	174
IL1A	ENSG00000115008	3.6	0.90934	6.7536426	0	180
IGF1	ENSG00000017427	3.6	0.90934	6.512027	0	202
VEGFA	ENSG00000112715	3.6	0.90934	14.649521	0	206
IL15	ENSG00000164136	3.6	0.90934	5.1354814	0	210
CCR5	ENSG00000160791	3.6	0.90934	22.46102	0	224
CDH1	ENSG00000039068	3.6	0.90934	3.7350864	0	226
IL17A	ENSG00000112115	3.6	0.90934	9.924029	0	233
CASP1	ENSG00000137752	3.6	0.90934	3.4077682	0	235
ICAM1	ENSG00000090339	3.6	0.90934	3.1813836	0	239
MAPK1	ENSG00000100030	3.6	0.90934	17.347782	0	251
MAPK3	ENSG00000102882	3.6	0.90934	24.315157	0	260
HSPD1	ENSG00000144381	3.6	0.90934	2.5022295	0	269
STAT1	ENSG00000115415	3.6	0.90934	25.515682	0	273
MMP3	ENSG00000149968	3.6	0.90934	2.4914422	0	275
IL10	ENSG00000136634	3.6	0.90934	2.4914422	0	277
IL5	ENSG00000113525	3.6	0.90934	2.2562785	0	288
CTNNB1	ENSG00000168036	3.6	0.90934	25.515682	0	294
TNF	ENSG00000232810	3.6	0.90934	2.2562785	0	296
CASP8	ENSG00000064012	3.6	0.90934	24.050282	0	300
MMP2	ENSG00000087245	3.6	0.90934	8.92919	0	324
STAT4	ENSG00000138378	3.6	0.90934	5.862493	0	326
MPO	ENSG00000005381	5.3999996	0.82925606	1.8166571	0.006	354
TGFB1	ENSG00000105329	3.6	0.90934	3.1813836	0	429
STAT3	ENSG00000168610	3.6	0.90934	13.903391	0	458
MAPK8	ENSG00000107643	3.6	0.90934	19.889582	0	460
IL13	ENSG00000169194	3.6	0.90934	5.862493	0	530
IL4	ENSG00000113520	3.6	0.90934	8.203337	0	532
IL18	ENSG00000150782	3.6	0.90934	3.7350864	0	535
NOS2	ENSG00000007171	3.6	0.90934	1.1343101	0	537
AKT1	ENSG00000142208	3.6	0.90934	15.6443615	0	541
KIT	ENSG00000157404	6.91	0.90934	6.7536426	0.039	573

Target Significance
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PASS Mechanisms
Interferon agonist,Interferon antagonist,Interferon gamma antagonist,Interferon inducer
Prostaglandin-E synthase inhibitor,Prostaglandin-E2 synthase 1 inhibitor
Interleukin 2 agonist,Interleukin 2 antagonist,Interleukin agonist,Interleukin antagonist
Cell adhesion molecule inhibitor,Selectin P antagonist,Selectin antagonist
Toll-Like receptor 2 agonist,Toll-Like receptor 2 antagonist,Toll-Like receptor agonist,Toll-Like receptor antago
Toll-Like receptor 4 antagonist,Toll-Like receptor agonist,Toll-Like receptor antagonist
Cell adhesion molecule inhibitor
Interleukin 8 antagonist,Interleukin agonist,Interleukin antagonist
Interleukin 12 agonist,Interleukin agonist,Interleukin antagonist
Interleukin 1 antagonist,Interleukin 1b antagonist,Interleukin agonist,Interleukin antagonist
Collagenase inhibitor,Gelatinase inhibitor,Matrix metalloproteinase inhibitor,Metalloproteinase inhibitor,Meta
Protein-serine-threonine kinase inhibitor,p21-activated kinase 1 inhibitor,p21-activated kinase inhibitor
Transcription factor STAT inhibitor,Transcription factor STAT6 inhibitor
Interleukin 6 antagonist,Interleukin agonist,Interleukin antagonist
Colony stimulating factor agonist,Colony stimulating factor antagonist,Granulocyte macrophage colony stimul
Interleukin 1 antagonist,Interleukin 1a antagonist,Interleukin agonist,Interleukin antagonist
Insulin like growth factor 1 agonist
Endothelial growth factor antagonist
Interleukin agonist,Interleukin antagonist
CC chemokine 5 receptor agonist,CC chemokine 5 receptor antagonist,CC chemokine receptor agonist,CC cher
Cadherin antagonist,Cell adhesion molecule inhibitor
Interleukin agonist,Interleukin antagonist
Interleukin 1 beta converting enzyme inhibitor
Cell adhesion molecule inhibitor,ICAM 1 antagonist
MAP kinase 1 inhibitor,MAP kinase inhibitor,MAP kinase stimulant
MAP kinase 3 inhibitor,MAP kinase inhibitor,MAP kinase stimulant
Chaperonin ATPase inhibitor
Transcription factor STAT inhibitor,Transcription factor STAT1 inhibitor
Matrix metalloproteinase 3 (membrane-type) inhibitor,Matrix metalloproteinase inhibitor,Metalloproteinase
Interleukin 10 agonist,Interleukin 10 antagonist,Interleukin agonist,Interleukin antagonist
Interleukin 5 antagonist,Interleukin agonist,Interleukin antagonist
Catenin beta inhibitor
Tumour necrosis factor alpha antagonist,Tumour necrosis factor alpha release inhibitor,Tumour necrosis facto
Caspase 8 inhibitor,Caspase 8 stimulant
Collagenase inhibitor,Gelatinase inhibitor,Matrix metalloproteinase 2 (membrane-type) inhibitor,Matrix meta
Transcription factor STAT inhibitor
Myeloperoxidase inhibitor,Peroxidase inhibitor
Transforming growth factor agonist,Transforming growth factor antagonist,Transforming growth factor beta 1
Transcription factor STAT inhibitor,Transcription factor STAT3 inhibitor
JNK mitogen-activated protein kinase inhibitor,MAP kinase 8 inhibitor,MAP kinase inhibitor,MAP kinase stimul
Interleukin agonist,Interleukin antagonist
Interleukin 4 antagonist,Interleukin agonist,Interleukin antagonist
Interleukin agonist,Interleukin antagonist
Inducible nitric oxide synthase inhibitor,Inducible nitric-oxide synthase inhibitor,Nitric-oxide synthase inhibitor
Protein kinase (PKA_comma_ PKC_comma_ AKT_comma_ GRK_comma_ AGC-related_comma_ RSK_comma_
Protein-tyrosine kinase (PTK_comma_ not ETK_comma_ WZC) inhibitor,Proto-oncogene tyrosine-protein kina

ating factor agonist,Granulocyte macrophage colony stimulating factor antagonist,Hydrolase inhibito

. agonist,Transforming growth factor beta 1 antagonist,Transforming growth factor beta agonist,Tran

. DBF2_comma_ SGK) inhibitor,Protein kinase B alpha inhibitor,Protein kinase B inhibitor,Protein kina

se B stimulant,Protein-serine-threonine kinase inhibitor