Molecular Pharmacology Fast Forward. Published on December 16, 2013 as doi: 10.1124/mol.113.089821

Title Page

Novel small molecule inhibitors of TLR7 and TLR9: mechanism of action and efficacy *in vivo*

Marc Lamphier, Wanjun Zheng, Eicke Latz, Mark Spyvee, Hans Hansen, Jeffrey Rose, Melinda Genest, Hua Yang, Christina Shaffer, Yan Zhao, Yongchun Shen, Carrie Liu, Diana Liu, Thorsten R Mempel, Christopher Rowbottom, Jesse Chow, Natalie C. Twine, Melvin Yu, Fabian Gusovsky, Sally T. Ishizaka

Eisai Inc., 4 Corporate Drive, Andover MA, 01810 (M.L., W.Z., M.S., H.H., J.R., M.G., H.Y., C.S., J.Z., Y.S., C.L., D.L., C.R., J.C., N.C.T., M.Y., F.G., S.T.I.)

Department of Infectious Diseases and Immunology, University of Massachusetts, Worcester, MA and Institute of Innate Immunity, University of Bonn, Germany (E.L.)

Center for Immunology and Inflammatory Diseases and Center for Systems Biology, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, USA. (T.R.M)

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

Running Title Page

Running Title: Small Molecule TLR Inhibitors

Corresponding Author:

Sally T. Ishizaka
Phone: 978-837-4642
Fax: 978-837-4932
E-mail: sally_ishizaka@eisai.com

Text pages: 22 pages
Tables: 2 tables
Figures: 10 figures
References: 33 references
Abstract: 232 words
Introduction: 567 words
Discussion: 939 words

Non-standard abbreviations:

ANA	anti-nuclear antibodies
BMDCs	Mouse bone marrow-derived dendritic cells
dsDNA	double-stranded DNA
FITC	Fluorescein isothiocyanate
IL-6	Interleukin-6
LPS	lipopolysaccharide endotoxin
PAMPA	Parallel Artificial Membrane Assay
PBMCs	peripheral blood mononuclear cells
PE	phycoerythrin
pIC	poly inosine-cytosine
SLE	Systemic Lupus Erythematosus
TLR	Toll-like receptor

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

Abstract

The discovery that circulating nucleic acid-containing complexes in the serum of autoimmune lupus patients can stimulate B cells and plasmacytoid dendritic cells via Toll-like receptors 7 and 9 suggested that agents that block these receptors might be useful therapeutics. We identified two compounds, AT791 and E6446, that inhibit TLR7 and 9 signaling in a variety of human and mouse cell types, and inhibit DNA - TLR9 interaction *in vitro*. When administered to mice, these compounds suppress responses to challenge doses of CpG-containing DNA, which stimulates TLR9. When given chronically in spontaneous mouse lupus models, E6446 slowed development of circulating anti-nuclear antibodies and had a modest effect on anti-double stranded DNA (dsDNA) titers, but showed no observable impact on proteinuria or mortality. We discovered that the ability of AT791 and E6446 to inhibit TLR7 and 9 signaling depends on two properties: weak interaction with nucleic acids and high accumulation in the intracellular acidic compartments where TLR7 and 9 reside. Binding of the compounds to DNA prevents DNA - TLR9 interaction *in vitro* and modulates signaling *in vivo*. Our data also confirms an earlier report that this same mechanism may explain inhibition of TLR7 and 9 signaling by hydroxychloroquine (Plaquenil), a drug commonly prescribed to treat lupus. Thus, very different structural classes of molecules can inhibit endosomal TLRs by essentially identical mechanisms of action, suggesting a general mechanism for targeting this group of TLRs.

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

Introduction

The Toll-like Receptors (TLRs) recognize a wide array of pathogen-associated and endogenous molecular patterns that trigger innate immune responses (reviewed in Sasai and Yamamoto, 2013). Certain types of nucleic acids can provoke a robust innate immune response, and this recognition is mediated by cytoplasmic receptors such as RIG-I and AIM2 and by TLRs localized inside endosomes and lysosomes (Barbalat et al, 2011). The nucleic acid-recognizing TLRs include TLR3, which is activated by double-stranded RNAs, TLRs 7 and 8, which are activated by single-stranded RNAs and TLR9, which mediates responses to single-stranded DNAs. The intracellular localization of these TLRs appears to prevent their spontaneous activation by circulating nucleic acids (Barton et al, 2006), however under certain pathological conditions endogenous nucleic acids can overcome this barrier. The immune complexes found in sera of patients suffering from systemic lupus erythematosus (SLE) typically contain nucleic acids associated with various proteins such as antibodies, the chromatin-associated protein HMGB1, the antimicrobial peptide LL39, ribonuclear proteins and others. These associated proteins may protect the bound nucleic acid from degradation and/or facilitate their entry into the cell, as is the case for Fc receptor-mediated uptake of antibody-nucleic acid complexes (Leadbetter et al., 2002, Means et al, 2005). Once inside the endolysosomal compartments, the nucleic acid cargo can then stimulate the intracellular TLRs, priming the immune system for further generation of anti-self antibodies. This cycle of innate immune recognition, generation of self-antibodies, and enhanced immune complex formation is believed to contribute to the pathogenesis of SLE and possibly Sjogren's syndrome (Marshak-Rothstein et al., 2006), a finding confirmed in animal models treated with TLR7 and TLR9-competitive antagonist oligonucleotides (Barrat et al., 2007; Christensen et al., 2005). In addition, TLR-mediated pathological responses to nucleic acids may contribute to other pathologies, such as damage due to liver injury or lung infection,

pancreatitis, and graft-versus-host disease (Bamboat et al., 2010, Calcaterra et al., 2008, Hoque et al., 2011, Itagaki, 2011). Recent clinical data show that an injectable, synthetic, competitive oligonucleotide inhibitor of TLR9 has efficacy in psoriasis (Kimball et al., 2013).

The purpose of our work was to develop an orally available, non-oligonucleotide small molecule inhibitor of TLR9. We describe two small molecules, AT791 and E6446, that can potently inhibit not only TLR9 stimulation by DNA, but also block TLR7 stimulation by RNA in mouse cell lines and inhibit DNA-TLR9 interaction *in vitro*. These compounds are orally bioavailable in mice, and can inhibit short-term induction of inflammatory cytokines by DNA. In a mouse MRL/lpr spontaneous model of lupus, E6446 slowed the development of circulating anti-nuclear antibodies and modestly suppressed anti-dsDNA titers, although it showed no observable impact on proteinuria or mortality. E6446 has also recently been shown to be effective in preventing hyper-inflammation and lethality caused by the parasite *Plasmodium berghei* in a mouse model of cerebral malaria (Franklin et al, 2011).

As described in an earlier preliminary report (Ishizaka, 2008), we show here that these compounds utilize an unusual mechanism of action: they interact weakly with nucleic acids but accumulate to a sufficiently high concentration in acidic compartments in cells that this interaction becomes significant. We also observed that the antimalarials hydroxychloroquine and chloroquine utilize a similar mechanism to suppress TLR7 and 9, consistent with a recent report by Kuznik et al (2011). Thus, very different structural classes of molecules can inhibit endosomal TLRs by essentially identical mechanisms of action, suggesting a general mechanism for targeting this group of TLRs.

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

Materials and Methods

Animals. Female BALB/c, were obtained from Charles River Laboratories or Jackson Laboratories and DO11.10 and MRL/lpr-MpJ mice from Jackson Laboratories, and housed under standard conditions. All animal experimental work was performed under protocols approved by the Eisai Andover IACUC.

Reagents and Compounds. AT791 (3-(4-(6-(3-(dimethylamino)propoxy)benzo[d]oxazol -2-yl)phenoxy)-N,N-dimethylpropan-1-amine) and E6446 (6-(3-(pyrrolidin-1-yl)propoxy) -2-(4-(3-(pyrrolidin-1-yl)propoxy)phenyl)benzo[d]oxazole) were synthesized at Eisai Inc. and their structures are shown in Figure 1A. Hydroxychloroquine and chloroquine were purchased from Sigma (St. Louis, MO). Soluble TLR9-Fc was cloned, expressed in HEK cells, and purified as previously described (Latz et al., 2004). LPS was purchased from List Biological Laboratories or Sigma. R-848, CL-097 and Cytoxan was from Sigma. Monoclonal antibodies to dsDNA (clone BV 16-13) were from Millipore.

Oligonucleotides. Phosphothioate-modified DNA or RNA oligonucleotides were obtained from Sigma Genosys or Dharmacon. Sequences (5' to 3'): **CpG2006** (TCG TCG TTT TGT CGT TTT GTC GTT), **3X-CpG2006 (**a 3x concatamer of CpG2006), **CpG2216** (GGG GGA CGA TCG TCG GGG GG), **GpC2216 (**GGG GGA GCA TGC TGC GGG GG), **CpG1668** (TCC ATG ACG TTC CTG ATG CT), **CpG1417** (TCG TCG TTT TGT CG), **RNA40** (GCC CGU CUG UUG UGU GAC UC), **SL4 RNA** (GGG GGA CUG CGU UCG CGC UUU CCC CU). In some cases, RNA oligos were complexed with the cationic lipid DOTAP (Roche) to facilitate uptake by cells (Hemmi et al., 2004)

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

In Vitro Cell-Based Assessment. HEK293 fibroblast cells (American Type Culture Collection, Manassas, VA) containing an NF-kB-luciferase reporter were stably transfected with pcDNA3.1D/V5-His-TOPO plasmid (Life Technologies) expressing human TLR9 (directly inserted as a *Taq* polymerase-amplified PCR product) or TLR7 (vector pCMV6-XL5 expressing human TLR7 cDNA from Origene). RAW 264.7 cells were stably transfected with a lentivirus containing an NF-kB-luciferase reporter (SA Biosciences). Compounds were added to cells 30 min. before stimulation with phosphothioate-modified CpG DNA or RNA oligonucleotides, the small-molecule imidazoquinoline TLR7 agonists R-848 or CL-097, or the TLR4 agonist lipopolysaccharide (LPS). Luciferase reporter activity was assayed using Steadylight (Perkin-Elmer). HEK:TLR7 respond to the imidazoquinoline TLR7 agonists, but not to RNA/DOTAP complexes. RAW cells respond to DNA, RNA (with or without DOTAP), R-848, CL-097 and LPS. For oligonucleotide uptake experiments, RAW 264.7 cells were incubated for 15 minutes with biotinylated CpG2006 complexed to phycoerythrin-streptavidin (BD Biosciences), washed and then fluorescence was visualized by confocal microscopy (Leica SP5).

Primary Cell Assays. Compounds were assayed for the suppression of BALB/c mouse spleen IL-6 production in response to stimulation by oligonucleotide CpG1668. Each compound was added to dissociated splenocytes (5×10^5 per well in complete RPMI/10% FBS in a 96 well plate) before addition of TLR agonists. Cells were stimulated for 72 hrs and supernatants were removed for ELISA analysis of IL-6 (R&D Systems). Mouse bone marrow-derived dendritic cells (BMDCs) were generated by culturing BALB/c marrow cells in RPMI containing 100ng/ml Flt3 ligand for 7 days. 1×10^5 cells in 50ul were assayed for IL-6 production after overnight or 24 hour stimulation with various TLR ligands. For studies using human peripheral blood mononuclear cells (PBMCs), Ficoll-separated mononuclear

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

cells were isolated from healthy volunteer donors, washed, and plated with stimulatory oligonucleotide CpG2216 in complete RPMI for 72 hrs. Interferon in supernatant was quantified by ELISA (Pestka Biomedical Laboratories).

Antigen Presentation Assay: Splenocytes were isolated from DO11 mice, washed twice after RBC lysis and re- suspended with complete RPMI. $5x10^5$ cells/well were seeded in a 96-well plate, with 10 ng/ml OVA323-339 peptide (ISQAVHAAHAEINEAGR, MW 1773.9) or 300 μg/ml OVA protein (Sigma, MW 42.7 kDa) and serial dilutions of compound. The cells were cultured at 37°C, 5% CO2 for 48 hours. 150 μl/well supernatant was harvested and stored at -80°C for IL-2 ELISA. 100 μl lysis/substrate solution of ATPLite (PerkinElmer) was added into each well. The plate was incubated at dark for 10 min. at room temperature and luminescence measured with an Envision Plate Reader (PerkinElmer).

Microarray analysis E6446 (250nM or 1250nM) or media were added to wells containing 4 x 10^6 BDMCs. Cells were stimulated with 250nM CpG1668 or left untreated. After 4 hours, cells were harvested and total RNA was isolated using Qiagen RNeasy Mini Kit. GeneChip assay was performed using the Affymetrix Mouse Genome 430A 2.0 Array following the Affymetrix standard eukaryotic target preparation protocol using 1 μg of total RNA. Array data was normalized using standard RMA GeneData Refiner workflow. All statistical analyses were calculated in GeneData Analyst. All probes were filtered based on arithmetic mean with a threshold at a signal of 100 across all samples. A two-group sample comparison test using a standard t-test was performed between CpG stimulated samples vs. medium control. All genes that were significantly regulated by CpG (uncorrected p-value <= 0.05 and fold change >=2) were reported, which included a total of 616 probe sets. Eight probe sets did not map to any known gene with the remaining mapping to a total of 461 known gene symbols. Comparisons between all treatments with medium control were performed. Relative

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

normalization method was applied to all the samples relative to the reference group (medium control). Two-dimensional hierarchical clustering using the 616 probe set signature was performed using GeneData Analyst using Manhattan distance and complete linkage.

Antibody-DNA complexes. Plasmid DNA (pcDNA3.1) was linearized with DdeI restriction enzyme and incubated with anti-DNA monoclonal antibody (Chemicon MAB030; clone BV 16-13) for 30 minutes in media before adding to wells containing 50,000 BMDCs. Cells were incubated overnight, and IL-6 was assayed the next day. Anti-biotin antibody (Jackson Labs) was used as a control antibody.

DNA uptake assay. RAW 264.7 cells (1 x 10^5 cells) were added to wells of a 96-well plate with glass cover slip bottoms (Mattek) and cultured overnight. One hour prior to stimulation, plates were pre-incubated at 4 ℃, 37 °C, or 37 °C in the presence of 1 μM AT791 or E6446. Biotinylated CpG2006 and streptavidin-linked phycoerythrin (PE) were mixed at a molar ratio of 8:1 (DNA:PE), and added to a final concentration of 200nM CpG2006/25nM PE and plates were further incubated at 4 ℃ or 37 °C. After 30 minutes, wells were washed with cold PBS and cells visualized by confocal microscopy.

Intracellular pH assay RAW 264.7 cells were incubated for 6 hours with 10 mg/ml of a mixture of fluorescein- and pHrodoRed- labelled ~ 10,000 MW dextrans (Life Technologies). Cells were washed 3X in Hank's buffer and AT791 (200nM), E6446 (200nM) or bafilomycin (10nM) were added for one hour. Cells were next visualized by confocal microscopy (Leica SP5). Fluorescein isothiocyanate (FITC; ex488/em525) and pHrodoRed (em563/ex585) fluorescence within intracellular vesicles were quantitated by intensities across line profiles.

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

After background subtraction, FITC:pHrodo intensity ratios of individual peaks (n>20) were calculated and averaged.

TLR9 – DNA interaction assay. Interaction between 20nM biotinylated CpG2006 oligonucleotide and 5 μg/ml Fc-tagged ectodomain of TLR9 was assayed using an Amplified Luminescent Proximity Homogeneous Assay system (ALPHA-Screen, Perkin-Elmer), as described in Latz et al. (2007). Assays were performed in pH5.5 acetate buffer, 150mM NaCl. Oligo CpG1417 is a 14-nucleotide DNA oligomer that does not detectably interact with Fc-TLR9 in this assay (data not shown).

Compound-DNA interaction. Fluorescence spectroscopy (Hitachi F-2000) was used to monitor the intrinsic fluorescence of 100nM AT791 or E6446 in 50mM NaAce buffer (pH5.5), 150mM NaCl at 310nm excitation / 380nm emission. 400nM of 2-aminopurine was used as a control, as this compound has a very similar fluorescence spectra. Hydroxychloroquine and chloroquine (5 μM each) fluorescence were monitored in 50mM phosphate buffer (pH 7.2), 150mM NaCl at 330nm excitation / 375nm emission. pH7.2 was used as these compounds fluoresce poorly at lower pH. Various concentrations of CpG2006 DNA or RNA40 oligonucleotides were added to compound solutions, and the change in compound fluorescence as a function of DNA or RNA concentration was analyzed by non-linear regression analysis for fit to a one-site binding curve (GraphPad Prism). DNA interaction with AT791 and E6446 was also quantified using a plate-based equilibrium dialysis system (RED system; Pierce). Compounds (200nM) were added to two chambers separated by an 8kDa cutoff membrane and DNA (3X-CpG2006; 22kDa) was added at various concentrations to one of the chambers. After incubation overnight, the concentrations of compounds in each chamber were quantified by mass spectroscopic analysis, and this data

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

was analyzed by non-linear regression analysis similar to above.

Intracellular localization of compounds

For the visualization of intracellular AT791 and E6446, HEK293 cells were incubated with 1μM of each compound for 5-15 min at 37 ˚C. The cells were then imaged using a Prairie Ultima IV multiphoton microscope system equipped with an Olympus 60x/1.15 numerical aperture water-immersion lens, and with a MaiTai HP and a MaiTai DeepSee laser (Spectra-Physics/Newport) providing excitation light at 920 nm and 707 nm, respectively. The HEK cells used in these experiments had been retrovirally transduced to stably express either Smad2-EGFP as a cytosplamic marker or LAMP-1 fused to EGFP as a lysosomal marker. AT791 was also visualized in cervical carcinoma C33A and CV-1 fibroblast cells by conventional confocal microscopy using a UV 351 nm laser ((Leica LSM SP2, courtesy of Owen Schwartz, NIH). Intracellular compound concentration was estimated by comparison to fluorescence obtained with known concentrations of AT791 spotted on microscope slides in pH5.5 buffer.

Parallel Artificial Membrane Permeation Assay (PAMPA). Five µl of a solution of 2% *L*-α-phosphatidylcholine in dodecane was deposited per well on membranes of a 96-well MultiScreen Permeability plate (Millipore; MAIPN4510). AT791 (10μM), E6446 (10μM), hydroxychloroquine (40μM) or chloroquine (40μM) were added to one of the two compartments in pH 5.5 buffer (50 mM NaAce, 150mM NaCl) or pH 7.4 buffer (50mM KPO4, 150mM NaCl), and the plate was incubated at 37 °C. The next day, compound concentrations in both chambers were quantitated. In one variation of this experiment, 5μM AT791 or E6446 was added to both chambers, one of which contained pH5.5 buffer and the other pH7.4 buffer. The redistribution of compound between the two chambers was

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

monitored for 8 hours.

Drug Treatment in Oligo Challenge. Drug was dissolved in acidified water and administered orally (20mg/kg) 18 hours prior to subcutaneous challenge with CpG1668 (60 µg/head). Two hours after oligo challenge, blood was collected for measurement of IL-6 in serum. IL-6 ELISA kits from BD Bioscience were used according to manufacturer's instructions.

Drug Treatment in Spontaneous Lupus Models. MRL/lpr mice were dosed orally five times a week with 20mg/kg or 60mg/kg E6446 or 60 mg/kg hydroxychloroquine beginning at 5 weeks of age. Cytoxan was administered at 50 mg/kg i.p. every 10 days. A serum sample was taken immediately before the beginning of treatment to monitor changes in autoreactive antibodies. Subsequently serum samples were collected approximately monthly and analyzed for anti-dsDNA by ELISA after 1:500 dilution (Alpha Diagnostics) Body weights and urine samples were taken at the same interval, and proteinuria assessed by ChemStrips (Roche Diagnostics). Anti-nuclear antibodies (ANA) were assessed using commercially available HEp2 slide kits (Antibodies, Inc., Davis, CA), with serum diluted to 1:100 in kit buffer. ANA scores were read blinded.

Results

Inhibition of TLR9 and TLR7signaling by small molecule ligands

HEK293 cells expressing cloned human TLR9 and an NF-kB:luciferase reporter (HEK:TLR9 cells) were used to screen a compound library for small molecules that could suppress induction of NF-kB by stimulatory DNA (CpG2006). AT791 and E6446 (Fig. 1A) potently suppressed DNA stimulation of HEK:TLR9 cells, with EC50s of 40nM and 10nM,

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

respectively, but were significantly less effective at suppressing lipopolysaccharide endotoxin (LPS) stimulation of HEK:TLR4 cells (Table I) or R848 stimulation of HEK:TLR7 cells.

Dendritic cells play a critical role in the initial innate immune response leading to adaptive immunity. We therefore tested the ability of AT791 and E6446 to suppress induction of IL-6 by various TLR ligands in mouse bone marrow-derived dendritic cells (BMDC). As shown in Figure 1B, AT791 and E6446 potently inhibited IL-6 production induced by CpG2216, but were ineffective against induction by the TLR3 ligand poly inosine-cytosine (pIC). Surprisingly however, the ability of these compounds to suppress TLR7 was ligand-dependent: both AT791 and E6446 were potent inhibitors of IL-6 induction by RNA, but relatively poor inhibitors of IL-6 induction by the small molecule imidazoquinoline ligand R-848. Similar results were seen in mouse splenocytes (Table I). In human PBMCs, AT791 and E6446 could suppress both IL-6 and α-interferon production induced by CpG oligo (Table I). Thus, antagonism is observed across species and output cytokine responses. E6446 showed a modest but consistent superiority over AT791, and both were significantly more potent than hydroxychloroquine (Plaquenil), which is commonly prescribed in the treatment of lupus.

To better understand this antagonism, we examined mRNA expression in BMDCs by microarray analysis. Stimulation with CpG1668 for 4 hours caused a reproducible change in a large number of genes, many of which are involved in inflammation, NF-kB signaling or the interferon response, consistent with previous reports (Klaschik et al., 2007). Significantly, 250nM and 1.25μM E6446 completely suppressed all of the CpG oligo-induced changes in gene expression (Supplemental Figure 1 & Supplemental Data I), while these concentrations of E6446 alone had no observable effect on gene expression after 4 hours This suggests that

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

the compound acts at or upstream of signal initiation.

Inhibition of stimulation by immune complexes

Complexes of antibodies with DNA, RNA, chromatin and/or associated proteins are believed to be responsible for the aberrant induction of inflammatory cytokines in lupus patients, as demonstrated by the ability of immune complexes isolated from lupus patients to stimulate TLR7 and TLR9 in cell culture (Vallin et al, 1999, Means et al., 2005). We generated DNA-antibody complexes by incubating highly-purified plasmid DNA with an anti-DNA monoclonal IgG1 antibody. Neither DNA nor antibody alone significantly induced production of IL-6 in BMDCs, but when pre-incubated together, they synergistically stimulated IL-6 production (Fig. 2A). No stimulation was seen when anti-biotin antibody was substituted for anti-DNA antibody (Fig. 2A) and no stimulation was observed in BMDCs from TLR9 knockout mice (data not shown) Figure 2B shows that immune complex stimulation was inhibited by AT791. Thus, AT791 can inhibit stimulation of TLR9 by DNA-antibody complexes.

Antagonism does not involve inhibition of nucleic acid uptake or modulation of endosomal pH

Mouse RAW 264.7 cells transfected with an NF-kB-responsive luciferase reporter were stimulated by CpG2006 DNA, SL4 RNA, CL-097 or LPS. Stimulation by CpG2006 or SL4 RNA, but not by LPS or CL-097, was completely suppressed with 100nM of AT791 or E6446 (Fig. 3, left 2 panels). To visualize uptake we generated complexes of biotinylated CpG2006 and streptavidin-linked phycoerythrin (PE-DNA), incubated these with RAW cells, and washed and examined the cells by confocal microscopy. No fluorescence was observed in cells that had been incubated with PE alone (data not shown), but fluorescence appeared as

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

intracellular punctate spots in cells incubated PE-DNA complexes at 37 degrees (Fig. 4). When PE-DNA was incubated with cells at 4 degrees, fluorescence was confined to the cell surface. Uptake of PE-DNA could also be blocked by the GTPase inhibitor Dynasore (data not shown). Pre-treatment of cells for 3 hours with 1μM AT791 or E6446 did not cause any visible change in subsequent DNA-PE complex uptake or localization.

Since both AT791 and E6446 are weak bases, we investigated whether they inhibit TLR7 and 9 by modulating endosomal pH. First, we compared inhibition by AT791 and E6446 versus known modulators of endosomal pH, bafilomycin, monensin and methylamine. As shown in Figure 3 (center panels), these pH modulators were all effective in inhibiting TLR7 and 9 signaling, however in contrast to AT791 and E6446, they show no selectivity for nucleic acid versus imidazoquinoline ligands. Next, changes in intracellular pH were monitored with dextran (10,000 MW) labeled with fluorescein isothiocyanate (FITC) and pHrodo (Life Technologies). Both of these dyes are pH-sensitive: FITC fluorescence decreases, and pHrodo fluorescence increases as pH decreases over the range pH 7.5 to pH 5.0, and the ratio of FITC:pHrhodo fluorescence can be used to indicate pH within this range. After loading with dextran complexes, RAW cells were incubated for ~ 3 to 4 hours with a concentration of each compound that resulted in >95% inhibition in the cell-based reporter assays. Cells were imaged by confocal microscopy and intracellular fluorescence was quantitated along line profiles. The pH modulators bafilomycin, monensin and methylamine produced a clear change in intracellular pH, whereas AT791 and E6446 had no obvious effect (Fig. 5, Supplemental Figure 2). 5μM hydroxychloroquine or chloroquine also had no measurable effect on intracellular pH, even though these concentrations can inhibit TLR9 or 7 signaling induced by DNA or RNA ligands, similar to observations reported by Manzel et al. (1999) and Kuznik et al (2011). Finally, we observed that 100nM AT791 had no significant effect on

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

OVA peptide presentation to DO11 T cells, a process that is inhibited by changes in endosomal pH (Supplemental Figure 3). Taken together, these data indicated that these compounds do not inhibit TLR7 and 9 signaling by modulation of endosomal / lysosomal pH.

DNA – TLR9 interaction assay

We next asked if these compounds could inhibit the interaction between TLR9 and DNA *in vitro*. We used an amplified luminescent proximity homogeneous system (AlphaScreen; Perkin Elmer) to detect an interaction between biotinylated CpG2006 oligonucleotide and the extracellular domain of TLR9 fused to immunoglobulin Fc-TLR9 (Latz et al., 2007), and found that E6446 and AT791 inhibited *in vitro* DNA – TLR9 interaction (Fig.6A). In a separate experiment, these compounds did not inhibit the interaction between Fc-tagged TLR2 and the biotinylated TLR2 ligand PamCysK (data not shown). The concentrations of AT791 and E6446 required to inhibit TLR9-DNA interaction are several orders of magnitude higher than those required to inhibit TLR7 or 9 signaling in cell cultures. However, when we examined a series of analogs of AT791 and E6446, we observed a good correlation between their potencies in the TLR9-DNA interaction assay and the cell-based assay (Supplemental Figure 4), suggesting that the ability of these compounds to disrupt DNA-TLR9 interaction *in vitro* is in some way related to their inhibition of TLR9 signaling.

Identification of drug target

We next asked which of the two components in the DNA-TLR9 interaction assay is the target of the compounds: DNA or TLR9? We imagined that if these compounds interact with DNA, it might be possible to alleviate inhibition by the addition of excess free oligonucleotide, which would compete for binding to the compound. This “oligo decoy” experiment requires that the competing oligonucleotide itself does not interact with TLR9. We identified a

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

non-TLR9-binding, non-signaling 14-nucleotide single-stranded oligonucleotide, CpG1417, that could be used as the decoy oligo (see Methods). We started with optimal amounts of biotinylated CpG2006 oligonucleotide and Fc-TLR9, and observed the expected inhibition by 10μM AT791 (Fig. 6B). However, when we added increasing amounts of CpG1417, the assay signal increased almost to the non-suppressed level. This data suggests that AT791 inhibits DNA – TLR9 interaction in vitro via an interaction with DNA and not with TLR9.

To confirm whether the interaction of compound with DNA is relevant to its ability to inhibit DNA – TLR9 interaction in cells, we developed a live cell version of the oligo decoy experiment. We created a non-stimulatory version of the oligo CpG2216 by inverting the stimulatory CpG motifs to GpC, to generate GpC2216. As shown in Figure 6D, the stimulatory CpG2216 induced Interleukin-6 (IL-6) production in BMDCs and this was inhibited by 10μM AT791. However, when an excess of the non-stimulatory GpC2216 was also added, induction of IL-6 was restored. GpC2216 itself, either alone or in the presence of AT791, did not stimulate IL-6 production (Fig. 6D). These results are consistent with the idea that suppression of TLR9 by AT791 involves an interaction of the compound with DNA.

Analysis of compound-DNA interaction

We analyzed compound-DNA interaction using fluorescence spectrometry and equilibrium dialysis. AT791 and E6446 are intrinsically fluorescent and have similar fluorescence spectra of 312nm peak excitation and 381nm peak emission (Supplemental Figure 5). Starting with 200nM AT791 or E6446, we added increasing amounts of CpG2006 or SL4 RNA and observed that compound fluorescence decreased in a quantitative and saturable manner (Fig. 6C). The same experiment using 2-aminopurine, a compound that has a similar fluorescence spectrum to AT791 and E6446, resulted in no change in fluorescence (Fig. 6C).

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

Changes in compound fluorescence as a function of nucleic acid concentration showed an almost perfect fit to a one-site binding curve (R^2>99%) with K_ds in the 1 ~ 4 μM range, similar to the IC_{50s} obtained in the in vitro DNA – TLR9 interaction assay (Fig. 6A). We confirmed these results using an equilibrium dialysis method with an 8 kDa cutoff membrane. AT791 (200nM) was added to both chambers and various concentrations of DNA (3X-CpG2006; 22kDa) were added to one chamber. After overnight incubation, compound concentrations in each chamber were quantitated by mass spectrometry. We obtained an almost perfect fit to a one-site binding curve (R^2=99.6%) and a Kd of ~ 3.4 μM (Supplemental Figure 6). In both the fluorescence quenching and equilibrium dialysis assays, DNA and RNA were in large molar excess over compound, thus the Kds here represent the binding of one drug molecule per oligonucleotide, although when higher concentrations of AT791 were mixed with CpG2006 and injected directly into a mass spectrometer, we could detect the binding of multiple drug molecules to the oligonucleotides (data not shown). By the fluorescence spectroscopy method we also found that the affinities of AT791 for the *in vitro* decoy oligo CpG1417 was 16μM +/- 3.2μM and that for the *in* vivo decoy oligo GpC2216 was 0.8μM +/- 0.1μM (data not shown).

To further test the idea that small molecule interaction with nucleic acids might be able to inhibit TLR signaling, we tested whether known DNA-binding molecules could inhibit TLR7 and 9. We found that the dimeric cyamine DNA dye YOYO-1 could suppress DNA- or RNA-induced signaling in a concentration-dependent manner (Fig. 3). Although YOYO-1 is relatively cell-impermeant, we observed that at high concentrations YOYO-1 fluorescence appeared in a punctate pattern in the cytoplasm of RAW 264.7 cells (data not shown). As seen for AT791 and E6446, YOYO-1 inhibits DNA- and RNA-induced signaling, but not imidazoquinoline- or LPS-induced signaling. Similar to these results, Kuznik et al (2011)

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

have also recently observed that TLR9 activation by stimulatory DNA can be inhibited by the DNA-binding dyes Hoechst 34580 and propidium iodide.

Compound localization and accumulation

The concentrations of AT791 and E6446 required to bind to nucleic acids and inhibit DNA-TLR9 interaction *in vitro* are at least 100x greater than the concentrations required to inhibit TLR7 or 9 signaling in cells, suggesting these compounds might accumulate in cells. Direct visualization of AT791 and E6446 in cells by conventional fluorescence microscopy is hampered by their low excitation wavelength (~310 nm), which does not transmit well through ordinary microscope glass. We used two methods to circumvent this limitation: two-photon microscopy, which uses 2x the normal wavelength to excite the fluorescent molecule, and high-intensity off-peak excitation with a 351 nm UV laser. When HEK cells were incubated with 1μM AT791 and visualized with two-photon excitation, compound fluorescence appeared within a few minutes as a punctate pattern in the cell cytoplasm (Fig. 7), and overlapped that of the lysosomal marker Lamp-1 (Supplemental Figure 7A). We observed a similar cytoplasmic punctate pattern in C33A cells incubated with 1μM AT791 and visualized by high-intensity 351 nm excitation (Supplemental Figure 7B). Comparing the intracellular fluorescence intensities to a calibration curve generated by spotting different concentrations of AT791 on a slide, we could estimate intra-vesicle AT791 concentration to be in the 1 to 2 mM range (Supplemental Figure 7B). These results indicate that AT791 and E6446 can accumulate several orders of magnitude inside lysosomes.

AT791 and E6446 are typical of “lysosomotropic” compounds in that they are lipophilic and contain weak base amines. At neutral pH, such compounds are non-polar and can penetrate lipid membranes, but within low pH vesicles they become protonated and are trapped

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

(DeDuve et al., 1974). Capillary electrophoresis showed that AT791 has pKas of 7.9 and 6.1, and E6446 has pKas of 8.6 and 6.5, indicating they would be more highly protonated in endolysosomal compartments compared to cytoplasm. We examined the pH-dependent lipid permeability of these compounds using a Parallel Artificial Membrane Assay (PAMPA) assay, which consists of two aqueous chambers containing pH7.4, 6.5 or 5.5 buffers, separated by a hydrophobic layer of *L*-α-phosphatidylcholine. In an overnight assay, the compounds readily penetrated the *L*-α-phosphatidylcholine layer at pH 7.4, but were almost completely non-permeant at or below pH 6.5 (Table II). We next established a pH gradient across the PAMPA membrane, adding pH5.5 buffer to one chamber and pH7.4 buffer to the other. Pilot experiments showed that this pH gradient can be maintained at least overnight. When 5 mM AT791 or E6446 were added to both chambers, we observed a steady re-distribution of the compounds into the pH5.5 compartment over 8 hours (Fig. 8). Thus the ability of these compounds to accumulate in low-pH compartments is an intrinsic chemical property. We observed that accumulation of these compounds in living cells occurred within minutes (Fig. 7). This rapid accumulation is presumably due to the very high surface-to-volume ratio of intracellular vesicles.

If accumulation of these compounds in endolysosomal compartments is necessary for their activity, they should be ineffective at inhibiting TLR7 or 9 localized elsewhere in the cell. We tested this idea using a receptor fusion between the TLR9 ectodomain and the TLR4 cytoplasmic domain (9N4C), which localizes to the cell surface and signals in response to stimulatory DNA (Barton et al., 2006). HEK cells expressing either full-length TLR9 or the 9N4C chimera were stimulated with CpG2006 oligonucleotides. We saw the expected inhibition of reporter activity by AT791 (1μM) in cells expressing full-length TLR9, but not in cells expressing 9N4C (Fig 9). Similar results were obtained with E6446 (data not shown).

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

In vivo efficacy

AT791 and E6446 are orally bioavailable (AT791, 41%; E6446, 20%) and have high volumes of distribution in mice (AT791, 12.8 L/kg; E6446, 95.9 L/kg). To test their activity *in vivo,* mice were orally dosed with 20mg/kg of AT791 or E6446, and 18 hours later were challenged with 60 µg CpG1668 oligonucleotide injected subcutaneously. CpG1668-induced IL-6 production was inhibited approx. 50% by AT791 and almost completely by E6446 (Fig 10A). We took the more active compound, E6446, and tested it in a MRL/lpr mouse SLE model. MRL/lpr females were dosed orally with 20 or 60 mg/kg of E6446 per day, five days a week, starting at one month of age. Anti-nuclear antibody (ANA) development was followed by immunofluorescence staining of Hep2 cells with the mouse sera and scoring for degrees of severity. Sera from untreated mice developed ANA reactivity gradually over the observation period, culminating in 11 of the 12 animals showing some degree of ANA-positivity by 18 weeks (Fig. 10B). In contrast, development of ANA was suppressed in a dose-dependent manner in animals treated with 20 mg/kg and at 60 mg/kg E6446. Examination of anti-double stranded DNA (dsDNA) titers gave a similar result, with E6446 partially suppressing the development of circulating anti-dsDNA antibodies in a dose-dependent manner (Fig. 10C). A control immunosuppressing agent cyclophosphamide (Cytoxan) effectively blocked autoantibody development (Fig. 10D). Although E6446 suppressed ANA development, we saw no suppression of proteinuria (data not shown).

Inhibition of TLR7 and 9 by antimalarials

Hydroxychloroquine (Plaquenil) is prescribed for the treatment of lupus, and both hydroxychloroquine and its analog chloroquine inhibit TLR7 and 9 signaling (MacFarlane & Manzel, 1998), results that we confirmed in Figure 3 (right panels) and Table I. We noticed a

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

number of similarities between the antimalarials and our compounds. Chloroquine interacts with double-stranded DNA (Cohen & Yielding, 1965) and accumulates in acidic compartments in cells (French et al., 1987). The antimalarials also exhibit a similar pattern of inhibition to AT791 and E6446: they more potently antagonize TLR7 signaling induced by RNA than the imidazoquinolines CL-097 or R-848 (Fig. 3, right panels and Table I). We therefore asked if these compounds might utilize a mechanism of action similar to that of AT791 and E6446 to inhibit TLR7 and 9 signaling. We observed that the intrinsic fluorescence of both antimalarials is quenched in the presence of CpG2006, and the data showed an excellent fit to a one-site binding curve with virtually identical Kds of 57μM +/- 5μM for both compounds (R^2 >99%) (Supplemental Figure 8). Given that the antimalarials have IC_{50} values in cell-based assays in the 1 ~ 5μM range, they would need to accumulate inside cells approximately 10 ~ 20-fold in order to achieve concentrations sufficient to interact with nucleic acids. In the PAMPA assay (Table II), both hydroxychloroquine and chloroquine were permeant at physiological pH, but non-permeant at pH 6.5 and below. Finally, neither hydroxychloroquine nor chloroquine produced any detectable change in intracellular pH at 5μM (Fig. 5), similar to the observations of Manzel et al (1999) and Kuznik et al. (2011). These data suggest that chloroquine and hydroxychloroquine may inhibit TLR7 and 9 signaling by accumulating inside cells and binding to nucleic acids, similar to AT791 and E6446, and not by modulation of pH. A similar conclusion was recently reported by Kuznik et al (2011) based on their studies of the antimalarials chloroquine and quinacrine.

Discussion

These data indicate that the ability of AT791 and E6446 to antagonize TLR7 and TLR9 signaling depends on two intrinsic properties: (1) their affinity for DNA, and (2)

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

accumulation in intracellular acidic compartments. It should be noted that the Kds for the interaction of these compounds with DNA is in the μM range, which is relatively weak. At the concentrations used to antagonize TLR7 and 9 in cells (10 ~ 50nM), there should be no significant interaction with DNA except in the intracellular vesicles where the compounds are concentrated. This localized action of the compounds may be beneficial, as it would limit potential off-target liabilities such as mutagenicity.

How does interaction of AT791 or E6446 with DNA inhibit TLR7 or TLR9 activation? As we observed *in vitro*, these compounds can interfere with DNA-TLR9 interaction. However, we found one analog of AT791 that enhanced DNA-TLR9 interaction *in vitro*, yet inhibited TLR9 activation in cell-based assays (data not shown), suggesting the involvement of other mechanisms of inhibition. DNA binding alone is not sufficient to activate TLR9, and certain DNA conformations and sequences, such as CpG motifs, are required to trigger a signaling event that is accompanied by a conformational change in TLR9 (Latz et al., 2007). Therefore, another way in which compounds such as AT791 and E6446 could inhibit TLR7 and 9 signaling is to render nucleic acids non-stimulatory by masking stimulatory sequences and/or altering their conformation.

AT791 and E6446 share several characteristics with a number of clinically approved lysosomotropic drugs such as haloperidol, levomepromazine and amantadine. All of these drugs are lipophilic, contain weak bases, exhibit high volumes of distribution *in vivo* and have long elimination half-lives. The accumulation of weak bases inside acidic vesicles has the potential to neutralize vesicle pH, and indeed chloroquine, methylamine and ammonium chloride are commonly used as biological reagents for this purpose. However, modulation of pH does not appear to explain inhibition of TLR7 and 9 signaling either by

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

AT791, E6446 or by the antimalarials chloroquine or hydroxychloroquine. First, we failed to see any significant effect of these compounds on endosome / lysosome pH using pH-sensitive fluorescent dyes. Strictly speaking, we do not know how the distribution of the TLR7 and 9 receptors overlaps with the dextran-containing, bright vesicles that we were able to visualize and quantitate. Furthermore, at concentrations higher than those used in the present study, AT791, E6446, chloroquine and hydroxychloroquine can all alter the fluorescence of both pH-sensitive and pH-insensitive fluorescent dyes, possibly due to direct molecular interactions between these molecules, e.g. hydrophobic ring stacking.

A stronger case is made by the distinct patterns of TLR7 antagonism caused by AT791, E6446, the antimalarials, known pH modulators and the DNA binding dye YOYO-1. These patterns of antagonism fall into two distinct groups: the known pH modulators antagonize TLR 7 activation by both RNA and imidazoquinoline ligands more or less equally, whereas AT791, E6446, the antimalarials, and YOYO-1 are highly selective for RNA versus the imidazoquinolines. Kuznik et al. (2011) also noted the selective antagonism of nucleic acid ligands by chloroquine, quinacrine and the DNA-binding dyes propidium iodide and Hoechst 34580. However, at higher concentrations, AT791, E6446, chloroquine and hydroxychloroquine can antagonize TLR7 induction by imidazoquinolines, probably because the accumulation of these weak bases is now sufficient to modulate endosomal pH. The window of selectivity between antagonizing RNA versus imidazoquinoline induction of TLR7 is 6~8-fold for chloroquine or hydroxychloroquine, and 20~40-fold for AT791 and E6446. This greater window of selectivity for AT791 and E6446 is presumably due to their higher affinity for nucleic acids. In SLE patients treated with daily doses of 200 ~ 400mg hydroxychloroquine, steady-state concentration of drug in the plasma has been reported to be in the range of 200 ~ 1000 ng/ml, or 0.4 ~ 2.0 μM (Tett et al., 1989). This is the

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

concentration range at which hydroxychloroquine can inhibit TLR7 and 9 in cell culture, but below the concentration required to alter endosomal pH. Indeed, hydroxychloroquine has been reported to be toxic in humans at a plasma concentration of 29 μM (Jordan et al, 1999). Thus, AT791 and E6446 may be considered more optimized versions of Plaquenil, functioning via the same mechanism of action to suppress TLR7 and 9 signaling, but providing a greater margin of selectivity.

In the spontaneous MRL/lpr mouse model of SLE, E6446 suppressed the development of anti-nuclear and anti-DNA antibodies, but not the development of glomerular nephritis. These results resemble those obtained with a $TLR9^{-/-}$ MRL/lpr mouse (Christensen et al., 2005). However, the role of TLR9 and TLR7 in the development of murine lupus is complex and may vary with the mouse model and experimental conditions. It has been reported that in some models TLR9 knockout can exacerbate lupus nephritis, that ablation of TLR7 is more effective at ameliorating disease, and that TLR9 modulates TLR7 activity (Wu et al., 2006, Christensen et al, 2006, Nickerson et al., 2010). A study using an oligonucleotide dual antagonist of TLR7 and TLR9 also reported efficacy in murine lupus models, showing reductions in anti-dsDNA titers in NZBxNZW and MRL models, and some positive impact on proteinuria and mortality (Barrat et al., 2007, Pawar et al., 2007).

Recently, Franklin et al (2011) have shown that E6446 is effective in preventing hyper-inflammation and lethality caused by the parasite *Plasmodium berghei* in a mouse model of cerebral malaria. Thus these compounds show efficacy in two very different animal models of disease driven in part by TLR activation. Taken together with the known efficacy of hydroxychloroquine and other antimalarials in human disease, the data presented here suggest a common mechanism of action for two structurally diverse families of endosomal

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

TLR inhibitors.

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

Acknowledgments

The assistance of the animal facility staff is gratefully acknowledged. All authors except E. Latz, and T. Mempel are or were employees of Eisai at the time this work was performed. Dr. Latz has participated in a previous sponsored research agreement with Eisai Research Institute. We thank Dr. Greg Barton (UC, Berkeley) for the HEK cell line expressing 9N4C, and Douglas Golenbock, Seiichi Kobayashi, Geoffrey Hird, Jiping Liu, Matthew Mackey and Lynn Hawkins for their helpful contributions and discussions. Portions of these results were presented at the meeting "Toll 2008: Recent Advances in Pattern Recognition" (Portugal, 2008).

Authorship contributions

Participated in research design: Lamphier, Zheng, Latz, Spyvee, Hansen, Zhao, Shen, Chow, Yu, Gusovsky, Ishizaka
Conducted experiments: Lamphier, Genest, Latz, Hansen, Rose, Yang, Zhao, Shen, C. Liu, D. Liu, Mempel, Rowbottom, Twine,
Contributed new reagents or analytic tools: Zheng, Latz, Shaffer, Shen, Mempel,
Performed data analysis: Lamphier, Latz, Hansen, Rose, Yang, Zhao, D. Liu, Mempel, Rowbottom, Twine, Yu, Ishizaka
Wrote or contributed to the writing of the manuscript: Lamphier, Mempel, D. Liu, Twine, Ishizaka

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

References

Barbalat R, Ewald SE, Mouchess ML, and Barton GM. (2011) Nucleic acid recognition by the innate immune system. *Annu Rev Immunol*. **29**:185-214

Bamboat ZM, Balachandran VP, Ocuin LM, Obaid H, Plitas G, DeMatteo RP. (2010) Toll-like receptor 9 inhibition confers protection from liver ischemia-reperfusion injury. Hepatology. **51**:621-632.

Barrat, F. J., T. Meeker, J. H. Chan, C. Guiducci, and R. L. Coffman. (2007) Treatment of lupus-prone mice with a dual inhibitor of TLR7 and TLR9 leads to reduction of autoantibody production and amelioration of disease symptoms. *Eur. J. Immunol*. **37**:3582-3586.

Barton GM, Kagan JC, and Medzhitov R. (2006) Intracellular localization of Toll-like receptor 9 prevents recognition of self DNA but facilitates access to viral DNA. *Nat Immunol* **7**:49–56

Calcaterra C, Sfondrini L, Rossini A, Sommariva M, Rumio C, Ménard S, Balsari A.(2008) Critical role of TLR9 in acute graft-versus-host disease. *J Immunol*. **181**:6132-6139.

Christensen, S.R., M. Kashgarian, L. Alexopoulou, R.A. Flavell, S. Akira, and M.J. Shlomchik. (2005). Toll-like receptor 9 controls anti-DNA autoantibody production in murine lupus. *J.Exp. Med*. **202**:321-331.

Christensen, S.R., J. Shupe, K. Nickerson, M. Kashgarian, R.A. Flavell, and M.J. Shlomchik. (2006) Toll-like receptor 7 and TLR9 dictate autoantibody specificity and have opposing inflammatory and regulatory roles in a murine model of lupus. *Immunity* **25**:417-428.

Cohen SN and Yielding KL (1965) Spectrophotometric Studies of the Interaction of Chloroquine with Deoxyribonucleic Acid. *J. Biol. Chem.* **240**: 3123-3131.

De Duve C, De Barsy T, Poole B, Trouet A, Tulkens P, Van Hoof F. (1974) Commentary. Lysosomotropic agents. *Biochem Pharm*. **23**:2495–2531.

Franklin BS, Ishizaka ST, Lamphier M, Gusovsky F, Hansen H, Rose J, Zheng W, Ataíde MA, de Oliveira RB, Golenbock DT, Gazzinelli RT. (2011) Therapeutical targeting of nucleic acid-sensing Toll-like receptors prevents experimental cerebral malaria. Proc Natl Acad Sci U S A. **108** :3689-3694.

French, JK, Hurst, N P, O'Donnell, M L, and Betts, W H (1987) Uptake of chloroquine and hydroxychloroquine by human blood leucocytes in vitro: relation to cellular concentrations during antirheumatic therapy. *Ann Rheum Dis*. **46**: 42–45.

Hemmi, H., T. Kaisho, O. Takeuchi, S. Sato, H. Sanjo, K. Hoshino, T. Horiuchi, H. Tomizawa, K. Takeda, and S. Akira. (2002) Small anti-viral compounds activate immune cells via the TLR7 MyD88-dependent signaling pathway. *Nat. Immunol*. **3**:196-200

Hoque R, Sohail M, Malik A, Sarwar S, Luo Y, Shah A, Barrat F, Flavell R, Gorelick F, Husain S, Mehal W. (2011) TLR9 and the NLRP3 inflammasome link acinar cell death with inflammation in acute pancreatitis. *Gastroenterology* **141**:358-369.

Itagaki K, Adibnia Y, Sun S, Zhao C, Sursal T, Chen Y, Junger W, Hauser CJ. (2011) Bacterial DNA induces pulmonary damage via TLR-9 through cross-talk with neutrophils. *Shock* **36**:548-552.

Ishizaka, S. (2008) Development and *in vivo* assessment of TLR9 inhibitors. Presentation at *Toll 2008: Recent Advances in Pattern Recognition* (Portugal, 2008).

Jordan, P., Brookes, J. G, Nikolic, G., Le Couteur, D. G., and Le Couteur, D. (1999) Hydroxychloroquine Overdose: Toxicokinetics and Management. *Clin Tox* **37:** 861-864.

Kimball A, Krueger J, Sullivan T, Arbeit R. (2013) IMO-3100, an antagonist of TLR7 and TLR9, demonstrates clinical activity in psoriasis patients with 4 weeks of treatment in a phase 2a trial. Abstract 158, International Investigative Dermatology, May 8-11, 2013.

Klaschik S., I. Gursel, and D.M. Klinman. (2007) CpG-mediated changes in gene expression in murine spleen cells identified by microarray analysis. *Mol. Immunol.* **44**:1095-1104.

Kuznik A, Bencina M, Svajger U, Jeras M, Rozman B, Jerala R. (2011). Mechanism of endosomal TLR inhibition by antimalarial drugs and imidazoquinolines. *J Immunol.* **186**:4794-4804.

Latz, E., A. Schoenemeyer, A. Visitin, K.A. Fitzgerald, B.G. Monks, C.F. Knetter, E. Lien, N.J. Nilsen, T. Espevik and D.T. Golenbock. (2004) TLR9 signals after translocating from the ER to CpG DNA in the lysosome. *Nat. Immunol*. **5**:190-198.

Latz, E., A. Verma, A. Visintin, M. Gong, C.M. Sirois , D.C. Klein, B.G. Monks, C.J. McKnight, M.S. Lamphier, W.P. Duprex, T. Espevik, and D.T. Golenbock. (2007) Ligand-induced conformational changes allosterically activate Toll-like receptor 9. *Nat. Immunol*. **8**:772-779.

Leadbetter EA, Rifkin IR, Hohlbaum AM, Beaudette BC, Shlomchik MJ, Marshak-Rothstein A. (2002) Chromatin-IgG complexes activate B cells by dual engagement of IgM and Toll-like receptors. *Nature* **416**:603–607.

MacFarlane, D.E., and L. Manzel. (1998). Antagonism of immunostimulatory CpG-oligodeoxynucleotides by quinacrine, chloroquine, and structurally related compounds. *J. Immunol*. **160**:1122-1131.

Manzel L., L. Strekowski, F. M. Ismail, J. C. Smith, D. E. Macfarlane. Antagonism of immunostimulatory CpG oligodeoxynucleotides by 4-aminoquinolines and other weak bases: mechanistic studies. (1999). *J Pharmacol Exp Ther*. **291**:1337-1347.

Marshak-Rothstein A. (2006) Toll-like receptors in systemic autoimmune disease. *Nat Rev Immunol*. **6**:823-835.

Means T.K., E. Latz, F. Hayashi, M.R. Murali, D.T. Golenbock, and A.D. Luster. (2005) Human lupus autoantibody-DNA complexes activate DCs through cooperation of CD32 and TLR9. *J. Clin. Invest*.115:407-417.

Nickerson KM, Christensen SR, Shupe J, Kashgarian M, Kim D, Elkon K, Shlomchik MJ. (2010) TLR9 regulates TLR7- and MyD88-dependent autoantibody production and disease in a murine model of lupus. *J Immunol*. **184**:1840-1848.

Pawar, R.D., A. Ramanjaneyulu, O.P. Kulkarni, M. Lech, S. Segerer, and H.-J. Anders. (2007) Inhibition of Toll-like receptor-7 (TLR-7) or TLR-7 plus TLR-9 attenuates glomerulonephritis and lung injury in experimental lupus. *J. Am. Soc. Nephrol.* **18**:1721-1731.

Sasai M, Yamamoto M. (2013) Pathogen recognition receptors: ligands and signaling pathways by toll-like receptors. *Int Rev Immunol*. **32**:116-133.

Tett, S. E., Cutler, D. J, Day, R O and Brown, K F. (1989) Bioavailability of hydroxychloroquine tablets in healthy volunteers. *Br J Clin Pharmacol*. **27**: 771–779.

Vallin, H., A. Perers, G.V.Alm, and L. Rönnblom. (1999) Anti-double-stranded DNA antibodies and immunostimulatory plasmid DNA in combination mimic the endogenous IFN-α inducer in systemic lupus erythematosus. J. Immunol. 163:6306-6313.

Wohnsland, F. and Faller, B. (2001) High-throughput Permeability pH Profile and High-throughput Alkane/Water Log P With Artificial Membranes, *J. Med. Chem.*, **44**:923–930.

Wu, X. and S.L. Peng. (2006) Toll-like receptor 9 signaling protects against murine lupus. *Arthitis Rheum.* **54**:336-342.

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

Legends for Figures

Figure 1. AT791 and E6446 structures and activities. A, Molecular structures. B, Suppression of Interleukin-6 production by mouse bone marrow-derived dendritic cells. Cells were treated with various concentrations of AT791 or E6446 and then stimulated overnight with the indicated agonists.

Figure 2. Interleukin-6 production by DNA-antibody complexes is suppressed by AT791. A, Anti-DNA antibodies and DNA synergistically stimulate production of IL-6 in mouse bone marrow-derived dendritic cells Anti-biotin antibody was used as a control. Data indicates that an optimal stoichiometry is required for efficient induction. B, Stimulation by DNA-antibody complexes is suppressed by AT791.

Figure 3. Selectivity of TLR inhibitors. RAW 264.7 cells containing an NF-κB:luciferase reporter were stimulated with optimal concentrations (approx. EC_{90}) of CpG1668 (DNA), RNA40 (RNA), CL-097 or LPS in the presence of a range of concentrations of the indicated inhibitors. After overnight incubation, luciferase activities were measured.

Figure 4. Uptake of OligoDNA – Phycoerythrin complexes by RAW 264.7 cells. DNA-phycoerythrin complexes are taken up by RAW264.7 cells within 30 minutes when incubated at 37 °C, but remain on cell surface when incubated at 4 °C. AT791 and E6446, even at a relatively high concentration (1 μM), have no obvious effect on complex uptake or localization

Figure 5. Effects of compounds on intracellular pH. Compound concentrations approximate the IC_{90} for inhibition of TLR9 stimulation in RAW264.7 cells. Cells were pre-loaded with dextrans conjugated to the pH-sensitive dyes FITC and pHrodo and fluorescence in intracellular vesicles was quantitated by confocal microscopy. Bafilomycin (BAF), methylamine (MA) and Monensin (MN) cause a significant increase in the FITC:pHrodo, indicating an increase in pH. In contrast, concentrations of AT791, E6446, chloroquine (CHL) or hydroxychloroquine (HCQ) sufficient to suppress TLR9 stimulation do not cause an increase in pH.

Figure 6. In vitro and in vivo characterization of AT791 and E6446. A. AT791 and E6446 suppress TLR9 – DNA interaction in vitro, with an IC_{50} in the 1 to 10μM range. B. Inhibition of TLR9-DNA interaction by AT791 can be relieved in the presence of an excess of a short competitor oligonucleotide CpG1417, which does not interact with TLR9. C. Addition of CpG2006 DNA (circles) or SL4 RNA (crosses) causes a quantitative change in the intrinsic fluorescence of AT791 and E6446, but not of a control compound 2-aminopurine. Fit to one-site binding curve (Graphpad Prism) gives Kμs in the 2 to 5 μM range (n=3), with R^2 goodness to fit >99%. D. Excess non-stimulatory oligoGpC2216 can relieve suppression of IL-6 production by AT791 in living cells (BMDCs).

Figure 7. Two-photon imaging of AT791 in living HEK cells. AT791 (1μM) was added to cultures of HEK cells and imaged 15 minutes later by two-photon microscopy. AT791 (red)

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

appears in a punctate pattern within the cytoplasm. Smad2-GFP is constitutively expressed and marks the cytoplasm.

Figure 8. pH partitioning of AT791 and E6446. AT791 and E6446 (5μM) were evenly distributed between chambers containing two different pH buffers and separated by a hydrophobic barrier. Over the next 8 hours, compounds re-distributed to the low pH compartment.

Figure 9: AT791 does not inhibit cell surface-expressed TLR9. A chimera consisting of the TLR4 cytoplasmic and transmembrane regions and the TLR9 ectodomain is expressed on the cell surface and induces NF-κB signaling in response to CpG2006 DNA. Whereas AT791 inhibits activation by the full-length, intracellular TLR9 (left panel), it has no effect on activation of the cell-surface expressed chimera (right panel).

Figure 10: In vivo efficacy of AT791. A. short-term induction of serum interleukin-6 in mice by CpG1668 DNA is effectively suppressed by pre-treatment with 20 mg/kg AT791 or E6446. Data are representative of two experiments. B. Anti-nuclear antibody (ANA) titers in 18-week old MRL/lpr mice are suppressed in a dose-dependent manner by E6446, given starting at week 5. Data representative of two experiments C. Development of anti-dsDNA antibodies in MRL-lpr mice is also suppressed by E6446. “pre” are serum samples taken before dosing at 5 weeks of age, “post” are samples taken after 7 weeks of E6446 dosing. Post-treatment samples are compared with vehicle control by one-way ANOVA with Newman-Keuls post-test. ** differs from vehicle with $p<0.01$, * differs from vehicle with $p<0.05$. Data representative of two experiments. D) Controls for experiments shown in panel C. Hydroxychloroquine (60 mg/kg, 5x per week) had no impact on anti-dsDNA, while cytoxan (50mg/kg, 1x per 10 days) caused a statistically significant suppression in titers. Statistical analysis as in C.

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

Table 1: Potency of small molecule inhibitors in engineered and primary cells

Responding Cells	**Stimulus**	**Readout**	**IC_{50} (μM)**		
			AT791	E6446	Hydroxy-chloroquine
HEK-TLR9	CpG2006	NF-kB – luc	0.04	0.01	0.08
HEK-TLR7	R848	NF-kB – luc	3.33	1.78	2.78
HEK-TLR4	LPS	NF-kB – luc	>10	10.58	>30
Mouse spleen	CpG1668	IL-6	0.04	0.02	3.1
	R848	IL-6	8.0	4.9	>10
	LPS	IL-6	8.9	N.D.	>10
Human PBMC	CpG2216	IL-6	0.21	0.23	1.2
		α-interferon	0.41	0.09	1.2
	CpG2006	IL-6	N.D.	0.28	N.D.

Luciferase reporter lines or primary mouse or human cells were stimulated overnight and activation assessed by NF-κB-luciferase reporter or cytokine ELISA as described in Materials and Methods. Results are the mean of 2 to 5 separate determinations. N.D. = not determined.

Molecular Pharmacology Fast Forward. Published on December 16, 2013 as DOI: 10.1124/mol.113.089821
This article has not been copyedited and formatted. The final version may differ from this version.

Table 2: Effect of pH on permeability of compounds

	Permeability (x 10^{-6} cm/s)		
	pH7.4	pH6.5	pH5.5
AT791	**58.5**	**0.1**	**0.2**
E6446	**67.4**	**0.3**	**0.4**
Hydroxychloroquine	**1.7**	**0.2**	**0.0**
Chloroquine	**19.5**	**3.7**	**1.4**

10μM AT791, 10 μM E6446, 40μM hydroxychloroquine, or 40 μM chloroquine in were assayed in a Parallel Artificial Membrane Permeation Assay, as described in Materials and Methods. Data represent the average of three replicates. Permeability was calculated according to Wohnsland & Faller (2001).

Figure 1

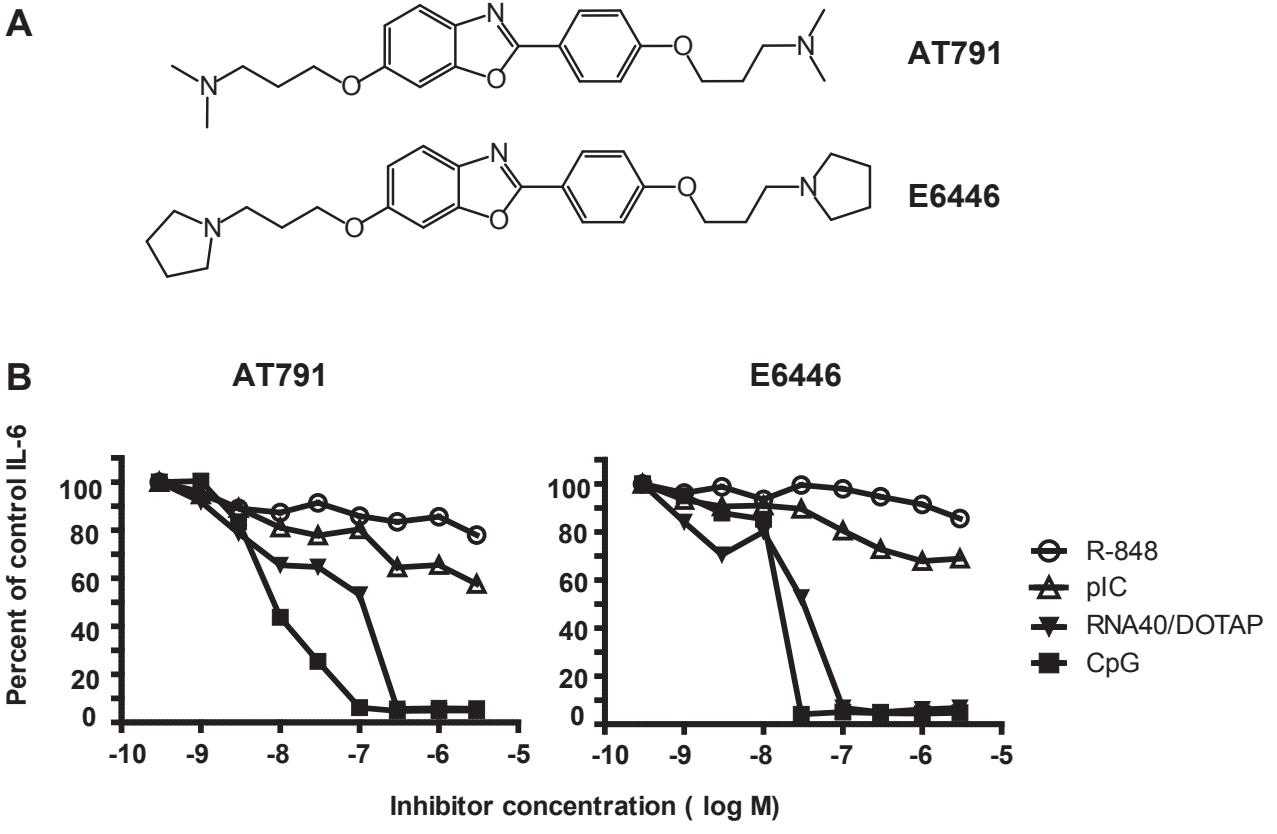

A
AT791
E6446
B
AT791
E6446
Percent of control IL-6
100
80
60
40
20
0
-10
-9
-8
-7
-6
-5
Inhibitor concentration (log M)
R-848
pIC
RNA40/DOTAP
CpG

Figure 2

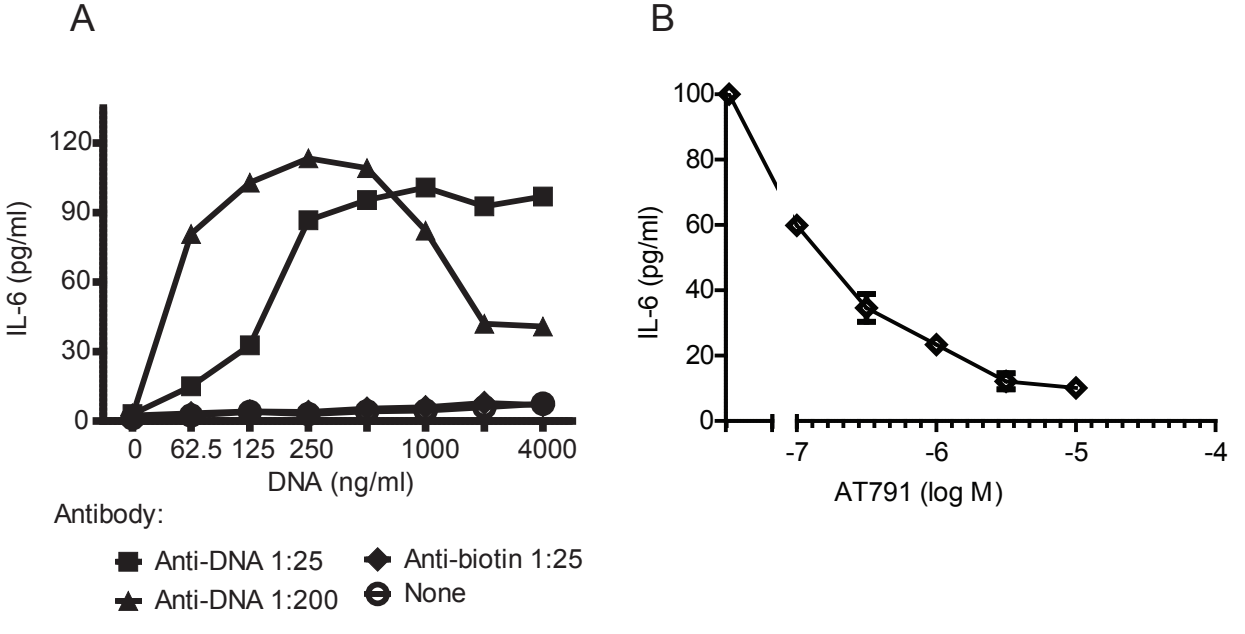

A
B
IL-6 (pg/ml)
120
90
60
30
0
0
62.5
125
250
1000
4000
DNA (ng/ml)
Antibody:
Anti-DNA 1:25
Anti-DNA 1:200
Anti-biotin 1:25
None
IL-6 (pg/ml)
100
80
60
40
20
0
-7
-6
-5
-4
AT791 (log M)

Figure 3.

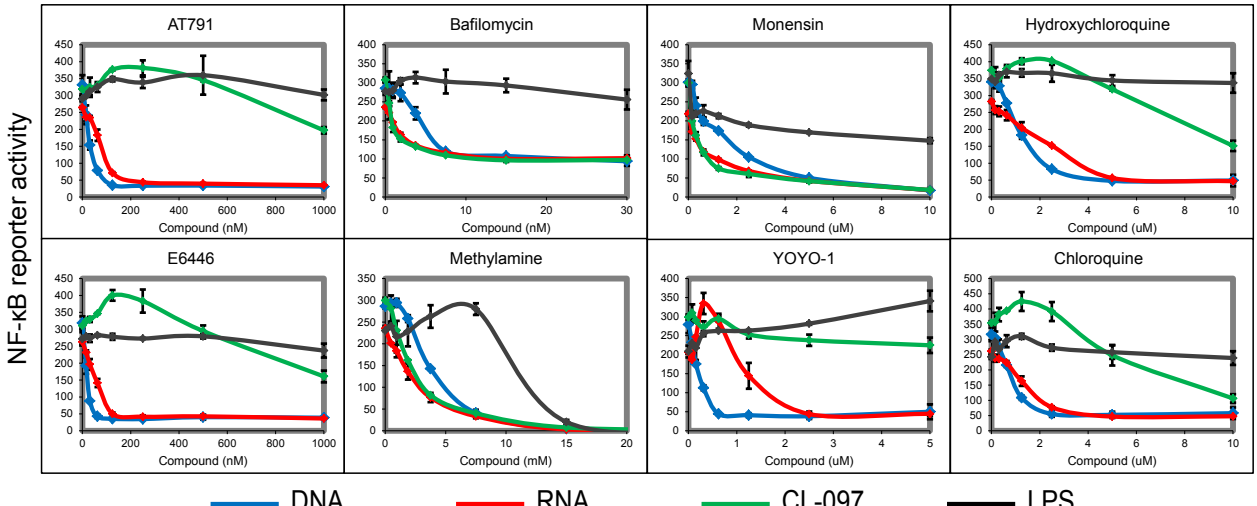
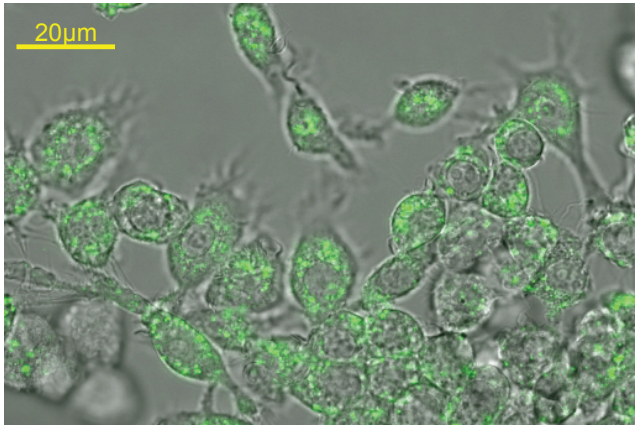
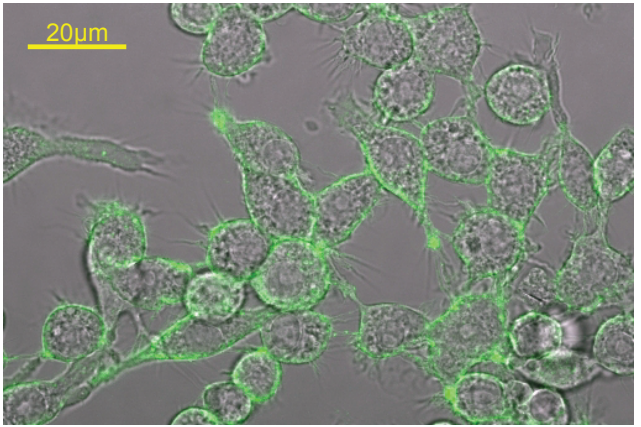

NF-κB reporter activity
AT791
Compound (nM)
Bafilomycin
Compound (nM)
Monensin
Compound (uM)
Hydroxychloroquine
Compound (uM)
E6446
Compound (nM)
Methylamine
Compound (mM)
YOYO-1
Compound (uM)
Chloroquine
Compound (uM)
DNA
RNA
CL-097
LPS

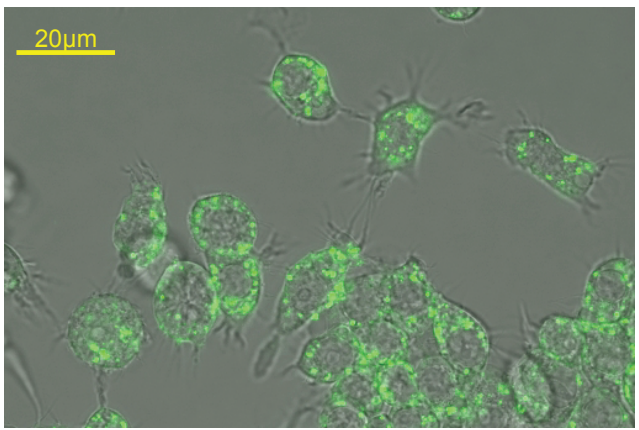
Figure 4



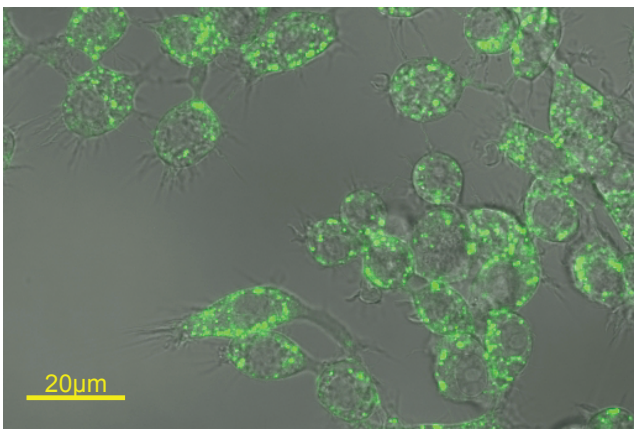
37°C



4°C



37°C - 1 µM E6446



37°C - 1 µM E6446

Figure 5

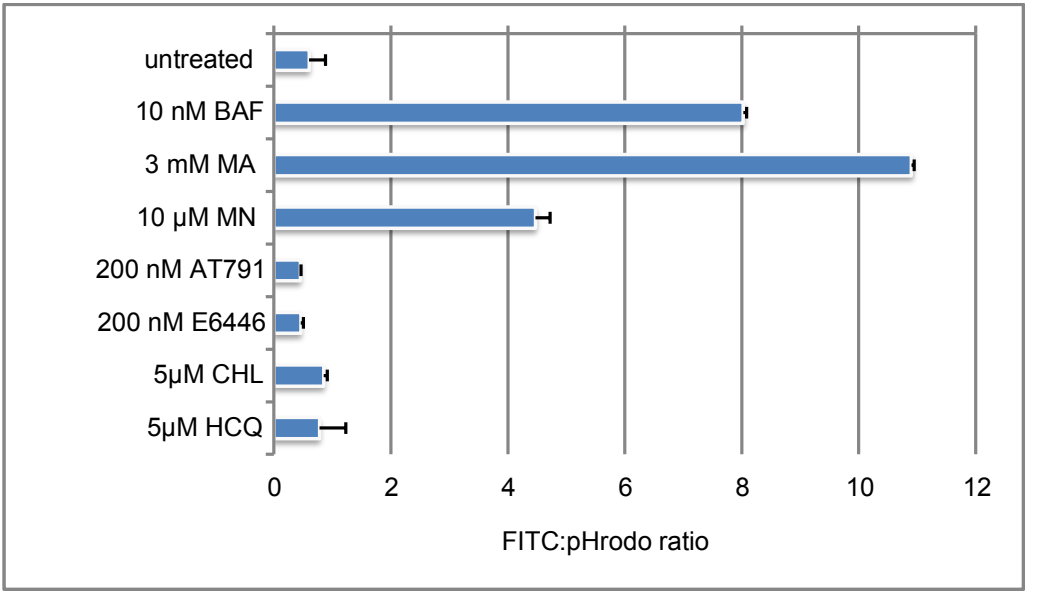
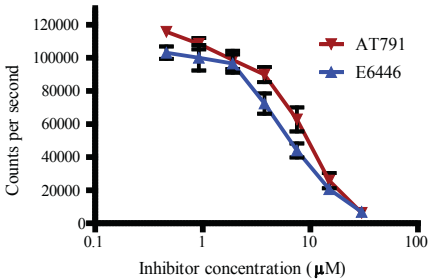
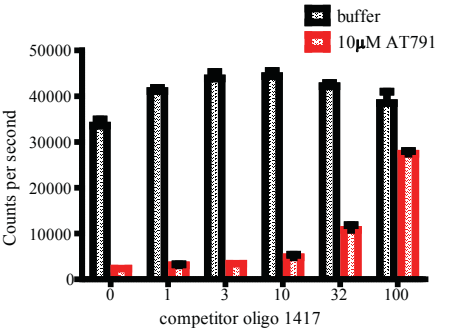

untreated
10 nM BAF
3 mM MA
10 µM MN
200 nM AT791
200 nM E6446
5µM CHL
5µM HCQ
0
2
4
6
8
10
12
FITC:pHrodo ratio

Figure 6

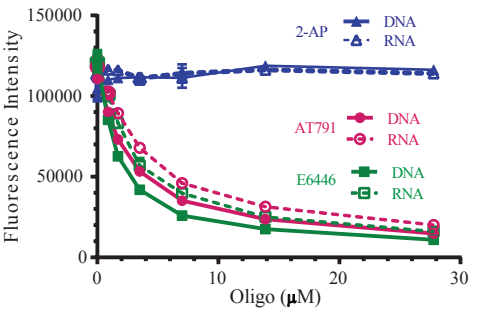
A



B

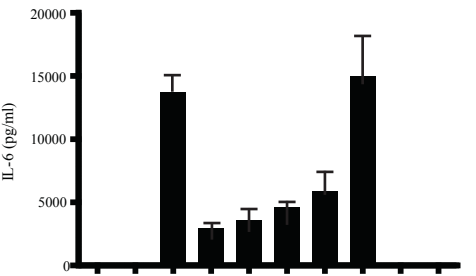


C



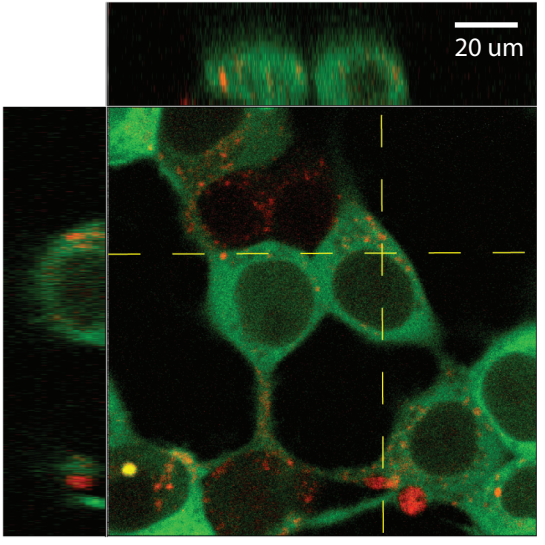
	DNA		RNA		Kds (μM)
AT791	2.5	(+/- 0.1)	3.6	(+/- 0.4)	
E6446	1.4	(+/- 0.2)	2.6	(+/- 0.3)	

D

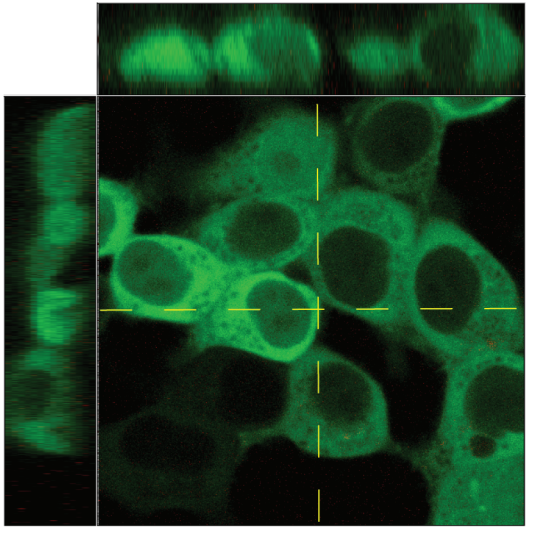


CpG 2216 (mM)	-	1.5	1.5	1.5	1.5	1.5	1.5	-	-
AT791 (mM)	-	-	1	1	1	1	1	1	-
GpC 2216 (mM)	-	-	-	1.25	2.5	5	10	10	10

Figure 7



1μM AT791 Smad2-EGFP



(control) DMSO Smad2-EGFP

Figure 8

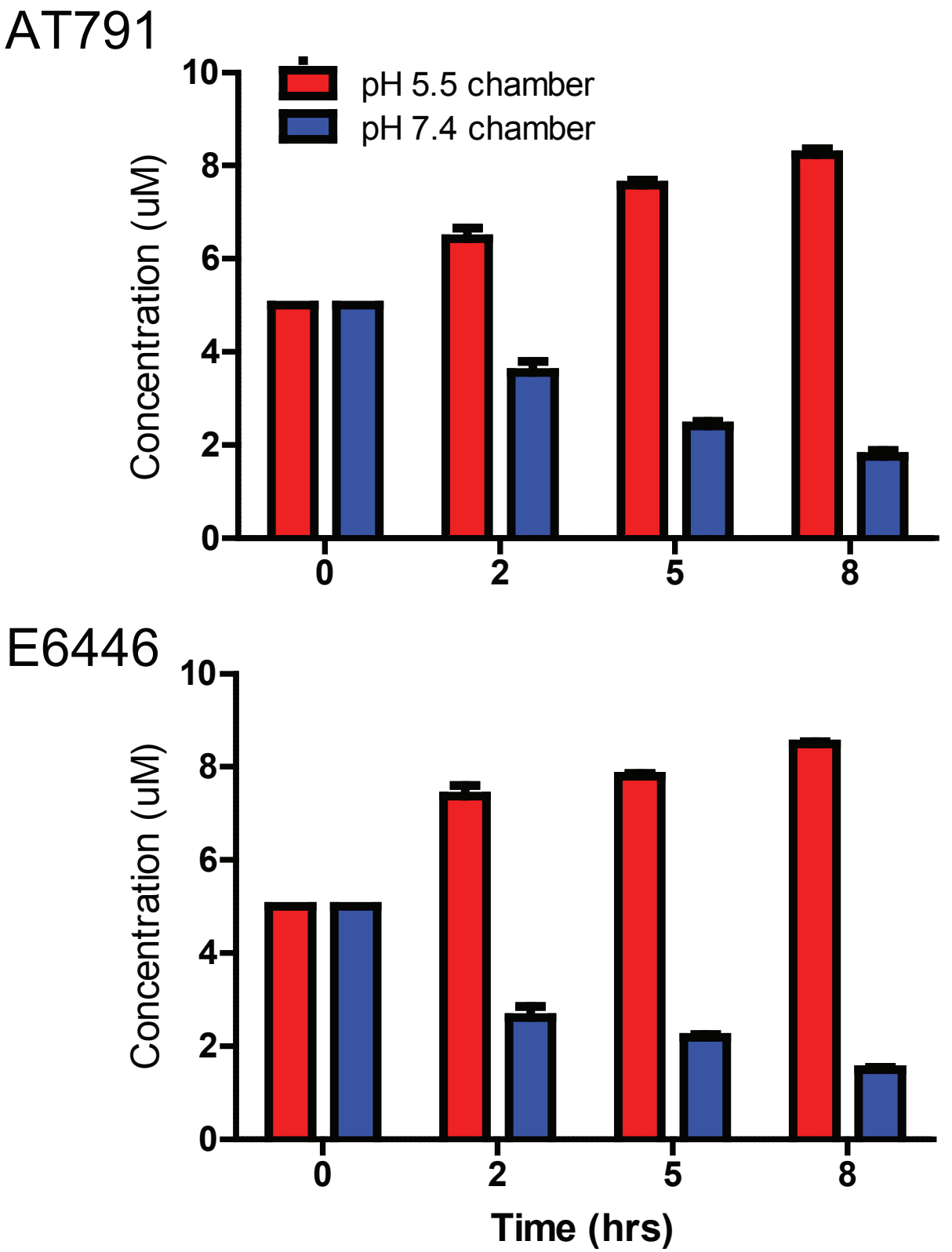

AT791
pH 5.5 chamber
pH 7.4 chamber
Concentration (uM)
10
8
6
4
2
0
0
2
5
8
E6446
Concentration (uM)
10
8
6
4
2
0
0
2
5
8
Time (hrs)

Figure 9

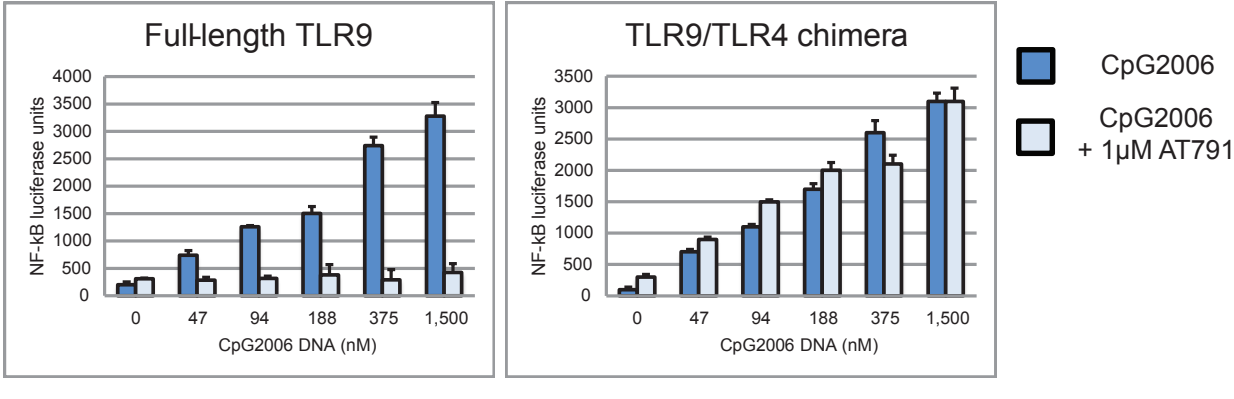
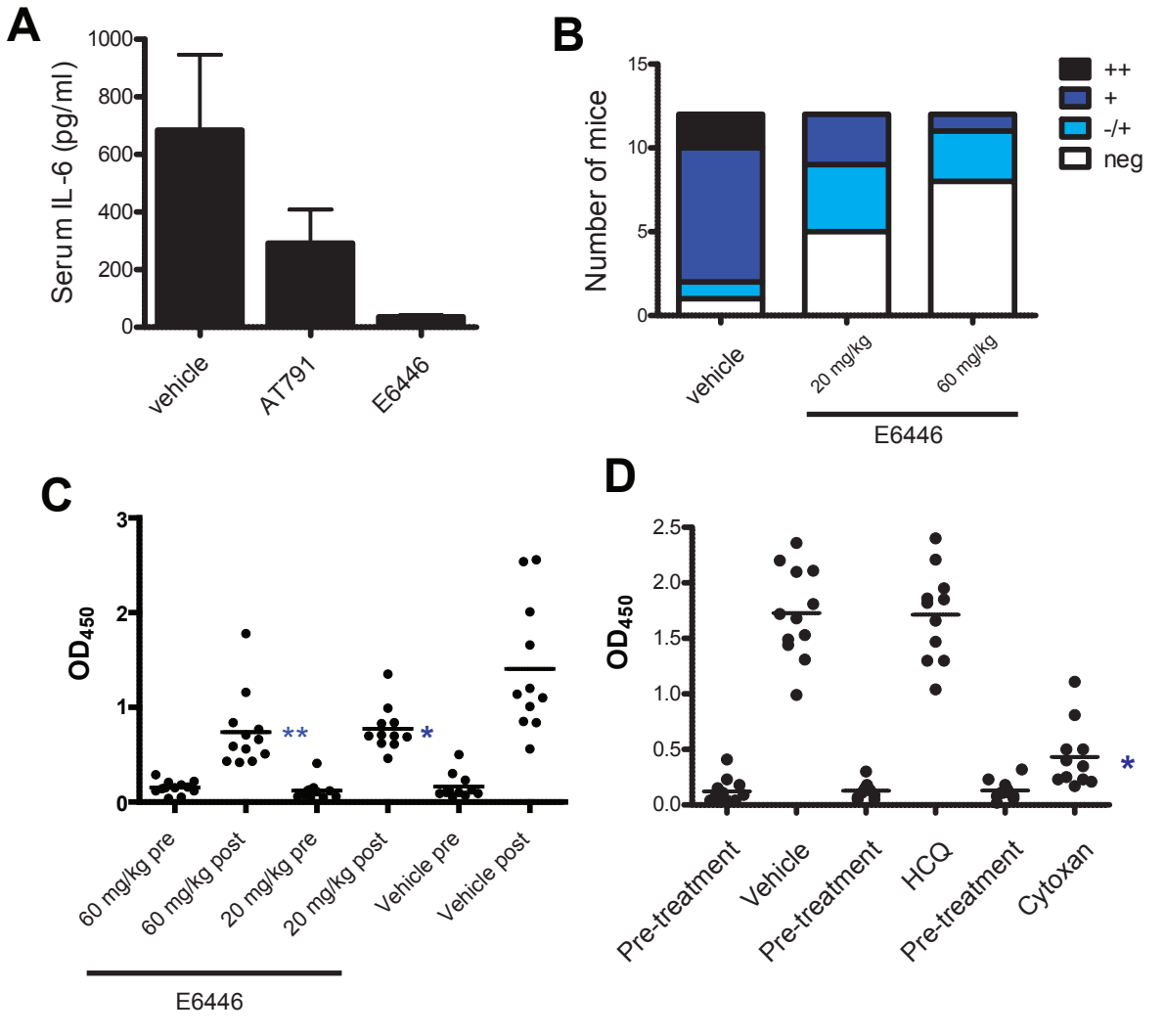
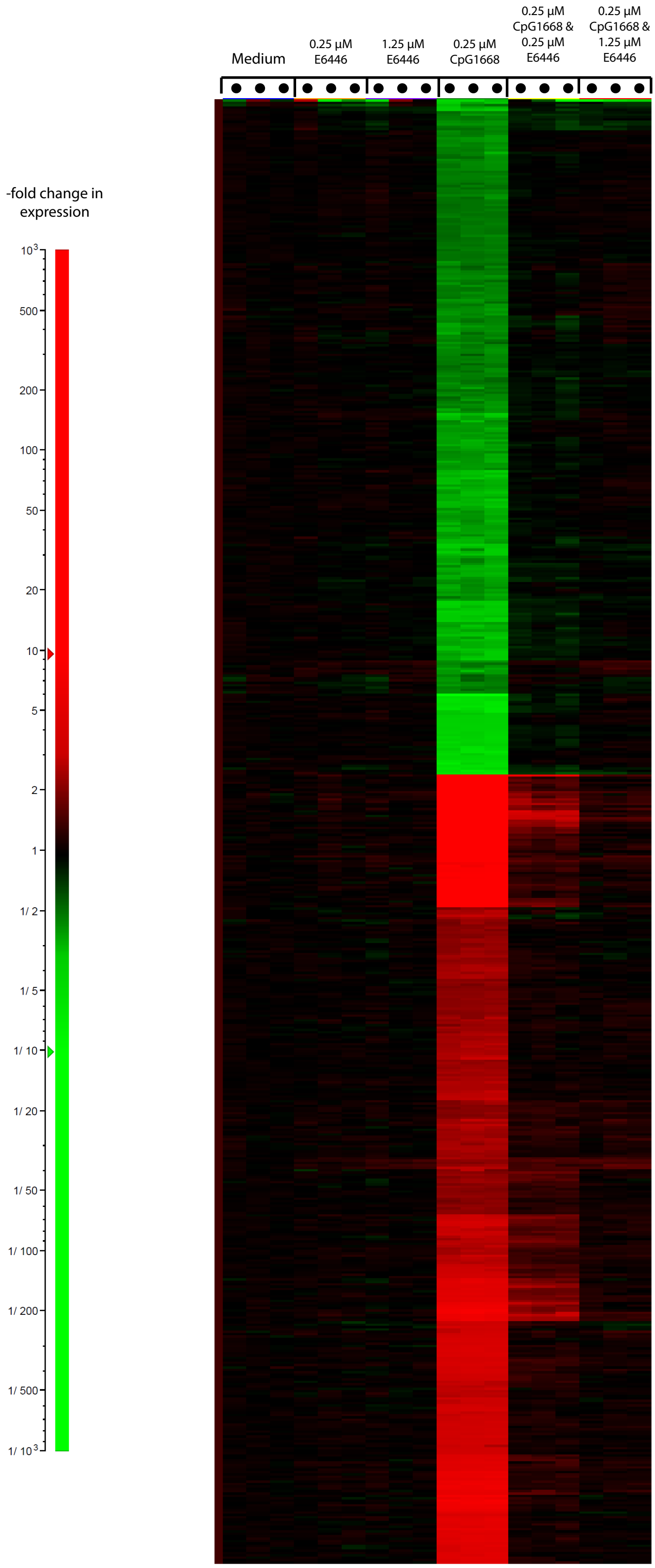

Full-length TLR9
NF-kB luciferase units
4000
3500
3000
2500
2000
1500
1000
500
0
0
47
94
188
375
1,500
CpG2006 DNA (nM)
TLR9/TLR4 chimera
NF-kB luciferase units
3500
3000
2500
2000
1500
1000
500
0
0
47
94
188
375
1,500
CpG2006 DNA (nM)
CpG2006
CpG2006
+ 1μM AT791

Figure 10


A
Serum IL-6 (pg/ml)
1000
800
600
400
200
0
vehicle
AT791
E6446
B
Number of mice
15
10
5
0
++
+
-/+
neg
vehicle
20 mg/kg
60 mg/kg
E6446
C
OD450
3
2
1
0
**
*
60 mg/kg pre
60 mg/kg post
20 mg/kg pre
20 mg/kg post
Vehicle pre
Vehicle post
E6446
D
OD450
2.5
2.0
1.5
1.0
0.5
0.0
*
Pre-treatment
Vehicle
Pre-treatment
HCQ
Pre-treatment
Cytoxan

Supplementary Figure 1: Analysis of genes modulated by CpG DNA and/or E6446

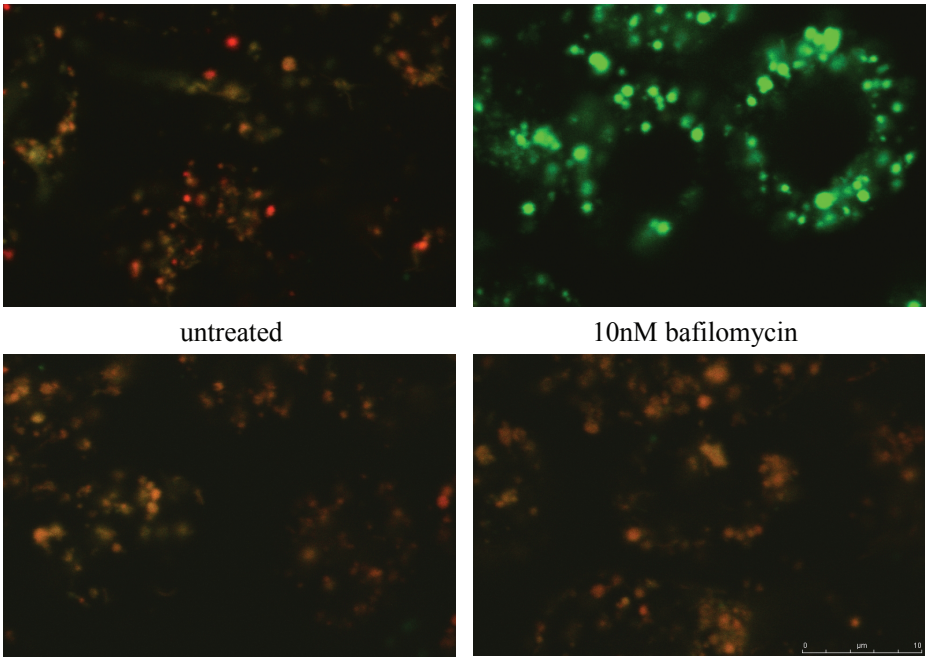


Supplementary Figure 1: Heat map shows increased (red) or decreased (green) expression of genes induced in BMDCs by 250nM CpG2116 in the presence or absence of the indicated concentrations of E6446 for 4 hours. Data shows three replicates for each condition for 616 probe sets, representing 461 known genes. Gene expression was analyzed by Affymatrix gene chip. Only genes whose expression was affected by either CpG1668 or E6446 are shown. Genes are ordered by hierarchical similarity clustering (not shown). Raw data is provided in Supplementary Data 1. The scale at them left indicates the –fold change in expression.

Novel small molecule inhibitors of TLR7 and TLR9: mechanism of action and efficacy in vivo
D. Liu, T. Mempel, C. Rowbottom, J. Chow, N. Twine, M. Yu, F. Gusovsky, S. Ishizaka

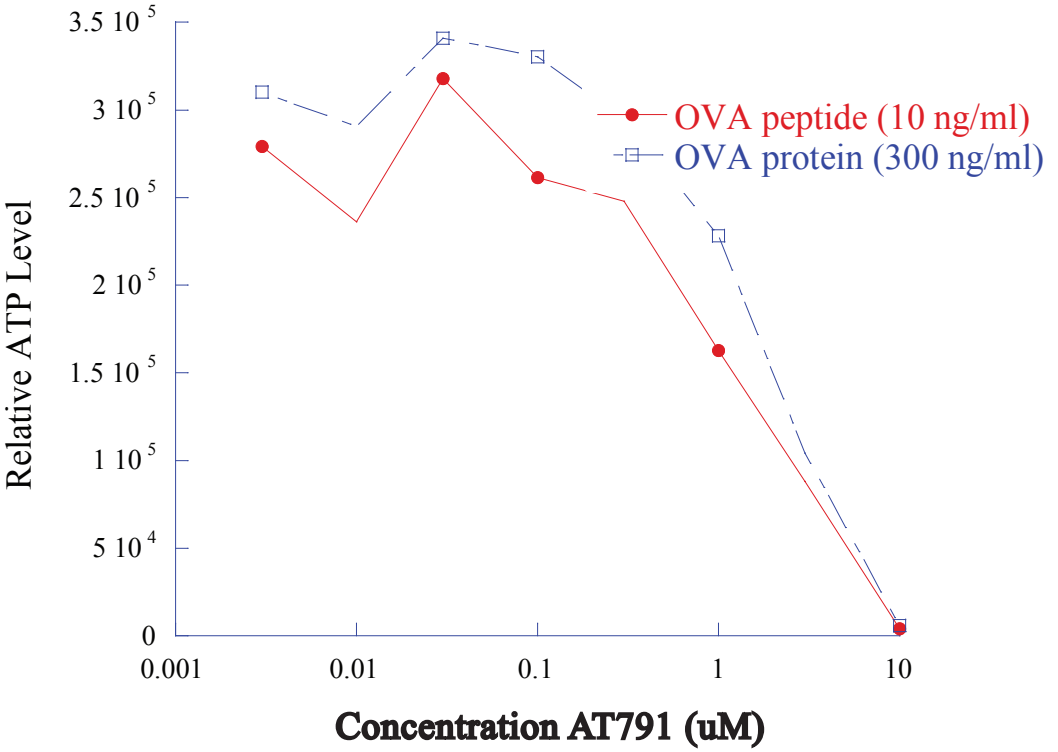
M. Lamphier, W. Zheng, E. Latz, M. Spyvee, H. Hansen, J. Rose, M. Genest, H. Yang, C. Shaffer, Y. Zhao, Y. Shen, C. Liu,
Journal: Molecular Pharmacology

Supplementary Figure 2: Effect of compounds on intracellular pH



Supplementary Figure 2: RAW264.7 cells were pre-loaded for 6 hours with dextrans conjugated to the pH-sensitive dyes FITC (green) and pHrodo (red). Next, cells were treated with the indicated compounds for one hour and visualized by confocal microscopy. Only bafilomycin caused an increase in pH, as indicated by a shift to green, caused by increased FITC fluorescence and decreased pHrodo fluorescence.

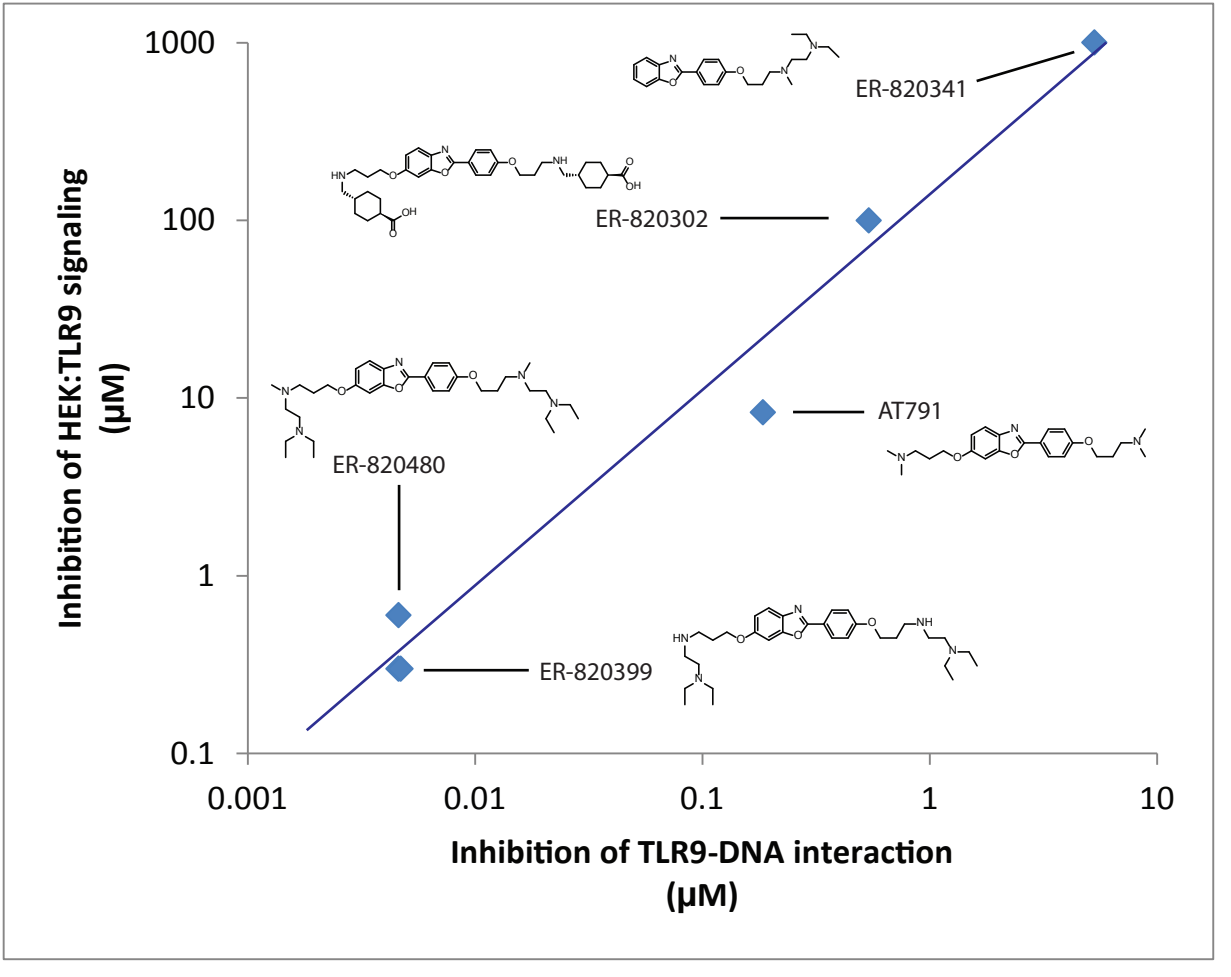
Supplementary Figure 3: Effect of AT791 on Class II antigen presentation in DO11 splenocytes



Supplementary Figure 3: DO11 mouse splenocytes were cultured with OVA peptide or protein for 2 days in the presence of the indicated concentrations of AT791. Two days later proliferation was assayed by ATP generation (ATPLite; Perkin Elmer).

Novel small molecule inhibitors of TLR7 and TLR9: mechanism of action and efficacy in vivo M. Lamphier, W. Zheng, E. Latz, M. Spyvee, H. Hansen, J. Rose, M. Genest, H. Yang, C. Shaffer, Y. Zhao, Y. Shen, C. Liu, D. Liu, T. Mempel, C. Rowbottom, J. Chow, N. Twine, M. Yu, F. Gusovsky, S. Ishizaka
Journal: Molecular Pharmacology

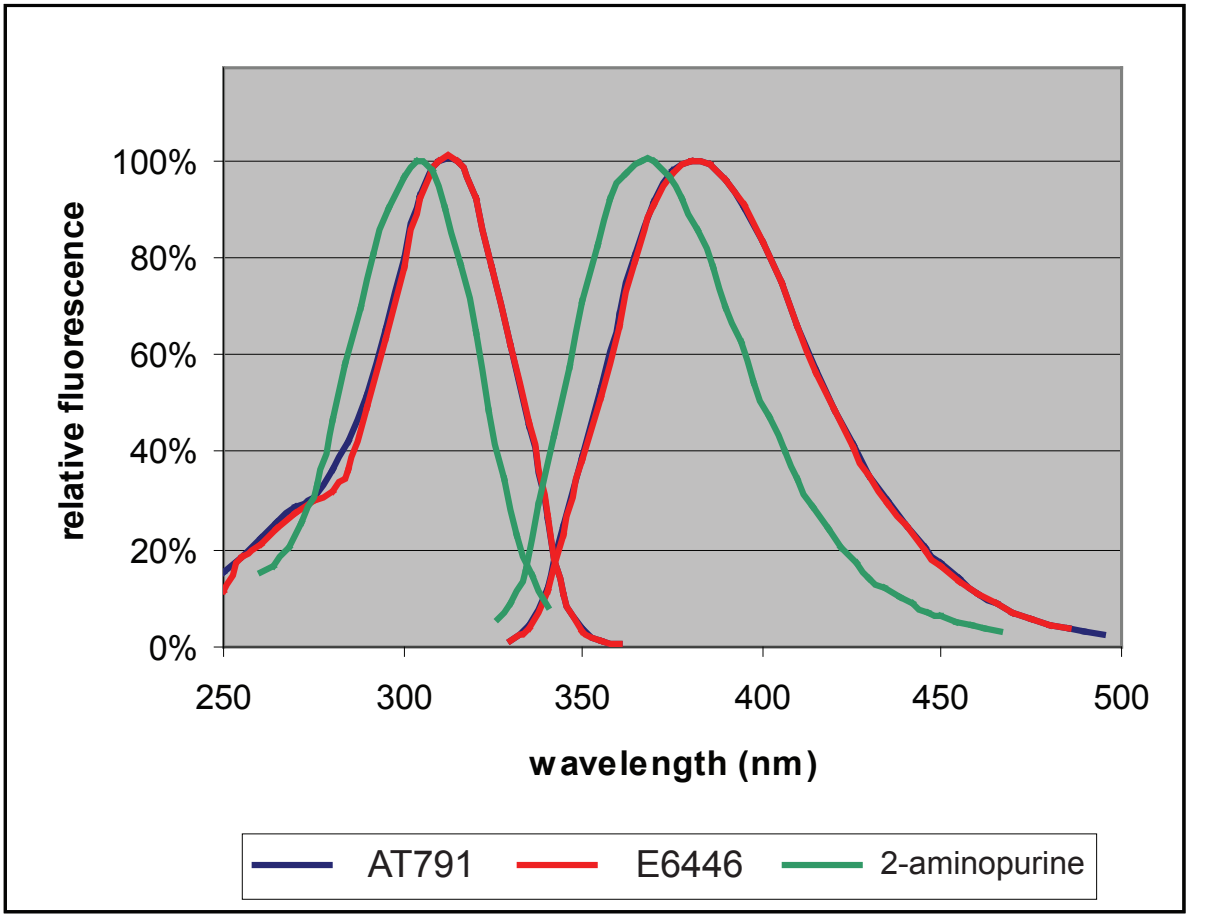
Supplementary Figure 4: correlation between compound *in vitro* and cell-based activities



Supplementary Figure 4: AT791 and other antagonists obtained in the same high-throughput screen were assayed in the TLR9-DNA interaction assay (in vitro) and in the HEK:TLR9 NF-κB reporter assay (cell-based). The plot shows the correlation between the in vitro and cell-based activities.

Novel small molecule inhibitors of TLR7 and TLR9: mechanism of action and efficacy in vivo M. Lamphier, W. Zheng, E. Latz, M. Spyvee, H. Hansen, J. Rose, M. Genest, H. Yang, C. Shaffer, Y. Zhao, Y. Shen, C. Liu, D. Liu, T. Mempel, C. Rowbottom, J. Chow, N. Twine, M. Yu, F. Gusovsky, S. Ishizaka Journal: Molecular Pharmacology

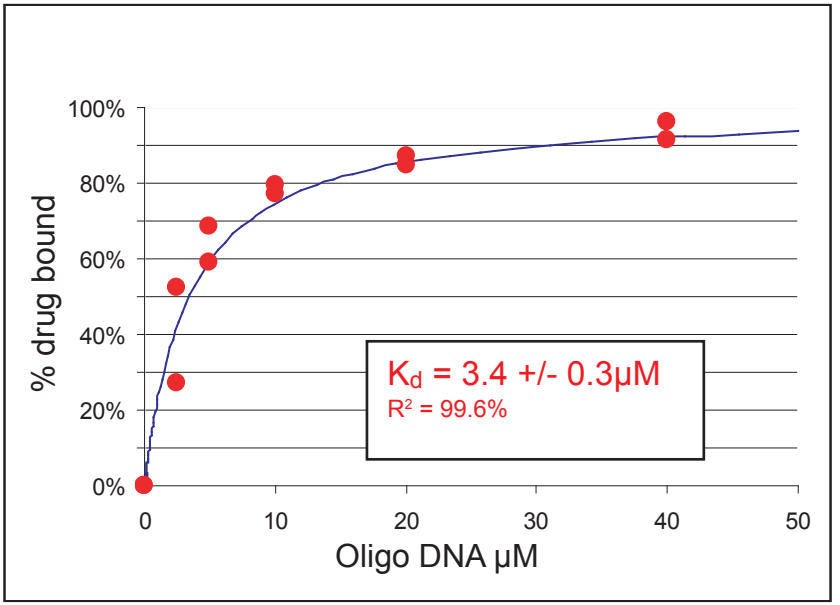
Supplementary Figure 5: Intrinsic fluorescence of AT791 and E6446



Supplementary Figure 5: Solutions of AT791, E6446 and 2-aminopurine were analyzed for fluorescence on a fluorescence spectrometer (Hitachi F-2000). The graph shows both the excitation and emission spectra. The spectra of AT791 and E6446 overlap almost completely, with peak excitation at 312nm and peak emission at 381nm. 2-aminopurine was found to have a fluorescence spectrum very similar to AT791 and E6446, and therefore used as a control in several experiments.

Novel small molecule inhibitors of TLR7 and TLR9: mechanism of action and efficacy in vivo M. Lamphier, W. Zheng, E. Latz, M. Spyvee, H. Hansen, J. Rose, M. Genest, H. Yang, C. Shaffer, Y. Zhao, Y. Shen, C. Liu, D. Liu, T. Mempel, C. Rowbottom, J. Chow, N. Twine, M. Yu, F. Gusovsky, S. Ishizaka
Journal: Molecular Pharmacology

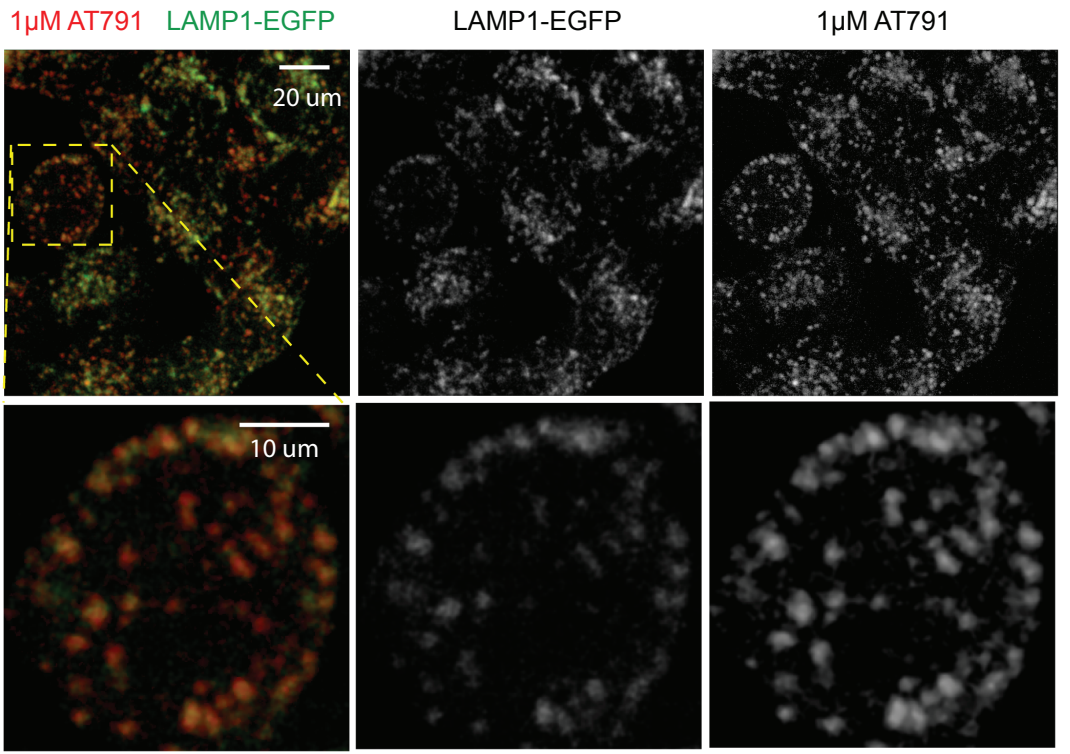
Supplementary Figure 6: Quantitation of AT791 - DNA interaction by equilibrium dialysis



Supplementary Figure 6: 200nM AT791 was added to both chambers of a plate-based equilibrium dialysis system (Pierce RED). 3x-2006 oligo (72nt; a 3x concatenated version of oligo CpG2006) was added at the indicated concentrations to one of the two chambers. After incubation for 4 hours at 37 °C, the amount of AT791 in each chamber was quantitated by mass spectrometry and the percentage of free versus bound compound in the DNA-containing chamber was calculated. The % bound was analyzed by non-linear regression analysis (GraphPad Prism) to fit to a one-site binding curve. Data shows results from two replicates, line represents fit to one-site binding curve as generated by Prism.

Novel small molecule inhibitors of TLR7 and TLR9: mechanism of action and efficacy in vivo M. Lamphier, W. Zheng, E. Latz, M. Spyvee, H. Hansen, J. Rose, M. Genest, H. Yang, C. Shaffer, Y. Zhao, Y. Shen, C. Liu, D. Liu, T. Mempel, C. Rowbottom, J. Chow, N. Twine, M. Yu, F. Gusovsky, S. Ishizaka
Journal: Molecular Pharmacology

Supplementary Figure 7A: Co-localization of AT791 with the lysosomal marker Lamp-1

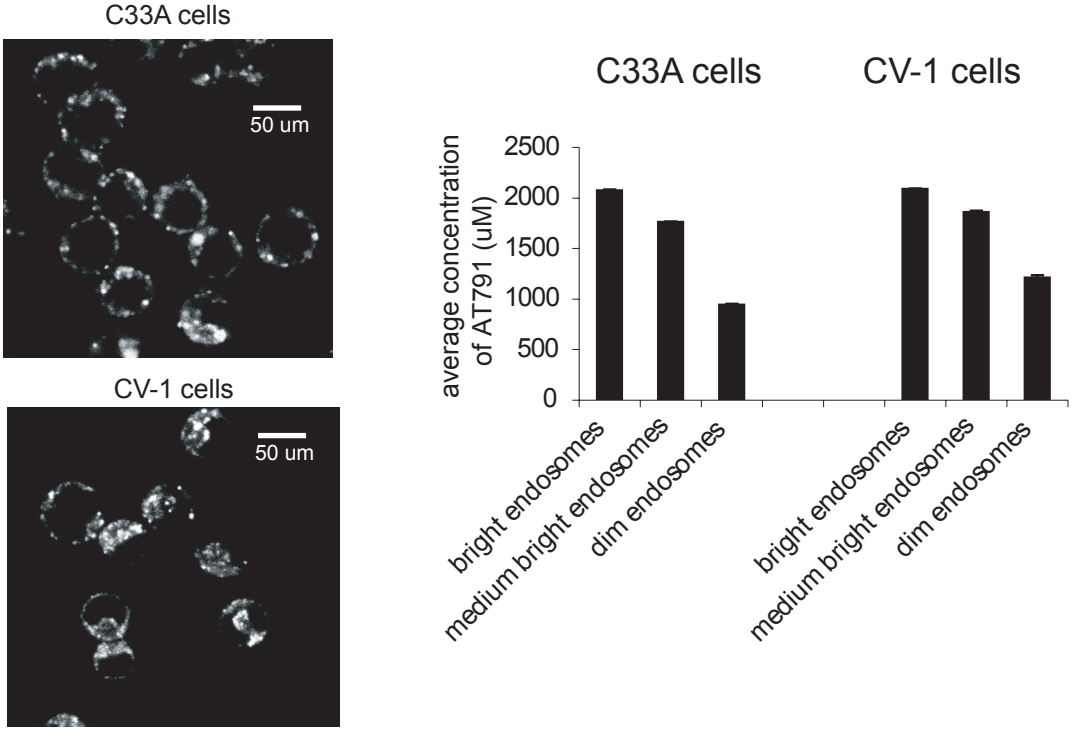


Localization of AT791 in HEK cells was visualized as shown in Figure 7, except that these HEK cells also expressed the lysosomal marker LAMP-1 fused to eGFP. Comparison of LAMP-1 and AT791 shows an overlap. AT791 on a glass slide. This analysis indicates that AT791 accumulates approximately 1,000-fold inside cells: from 1μM added to the culture media to

500 ~ 2000 μM inside vesicles.

Novel small molecule inhibitors of TLR7 and TLR9: mechanism of action and efficacy in vivo M. Lamphier, W. Zheng, E. Latz, M. Spyvee, H. Hansen, J. Rose, M. Genest, H. Yang, C. Shaffer, Y. Zhao, Y. Shen, C. Liu, D. Liu, T. Mempel, C. Rowbottom, J. Chow, N. Twine, M. Yu, F. Gusovsky, S. Ishizaka
Journal: Molecular Pharmacology

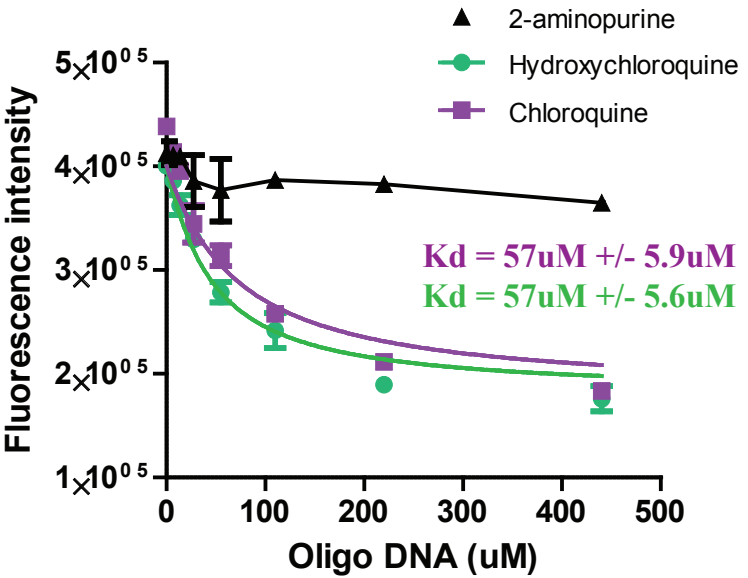
Supplementary Figure 7B: Quantitation of AT791 accumulation in C33A and CV-1 cells



AT791 (1μM) was added to cultures of C33A and CV-1 cells and visualized by confocal microscopy using a 351nm laser. Intracellular AT791 concentrations were estimated by comparing fluorescence intensities in intracellular vesicles to a calibration curve generated by spotting different concentrations of AT791 on a glass slide. This analysis indicates that AT791 accumulates approximately 1,000-fold inside cells: from 1μM added to the culture media to 500 ~ 2000 μM inside vesicles.

Novel small molecule inhibitors of TLR7 and TLR9: mechanism of action and efficacy in vivo M. Lamphier, W. Zheng, E. Latz, M. Spyvee, H. Hansen, J. Rose, M. Genest, H. Yang, C. Shaffer, Y. Zhao, Y. Shen, C. Liu, D. Liu, T. Mempel, C. Rowbottom, J. Chow, N. Twine, M. Yu, F. Gusovsky, S. Ishizaka
Journal: Molecular Pharmacology

Supplementary Figure 8: Fluorescence spectroscopic analysis of DNA interaction with hydroxychloroquine and chloroquine



Fluorescence of hydroxychloroquine and chloroquine (5 µM each) were quantitated at excitation 330nm and emission 375nm in pH7.2 buffer. CpG2006 oligo DNA was added at a range of concentrations as indicated and the change in intrinsic compound fluorescence was measured. As a control, 2-aminopurine was used, as it has a similar fluorescence spectrum. Non-linear regression analysis showed an excellent fit to a one-site binding curve with similar Kds of 57µM for both compounds.

Novel small molecule inhibitors of TLR7 and TLR9: mechanism of action and efficacy in vivo

M. Lamphier, W. Zheng, E. Latz, M. Spyvee, H. Hansen, J. Rose, M. Genest, H. Yang, C. Shaffer, Y. Zhao, Y. Shen, C. Liu, D. Liu, T. Mempel, C. Rowbottom, J. Chow, N. Twine, M. Yu, F. Gusovsky, S. Ishizaka

Journal: Molecular Pharmacology

Supplemental Data 1: detailed list of genes analyzed in Supplemental Figure 1

(see Supplemental Figure 1 for legend)

							Stimulation Only		Compound Only				Stimulation and Compound			
Probe Set Description							CpG vs. Medium		0.25 uM E6446 vs. Medium		1.25 uM E6446 vs. Medium		CpG + 0.25 uM E6446 vs. Medium		CpG + 1.25 uM E6446 vs. Medium	
Row	Notes	Symbol	Entrez Gene Name	Location	Type(s)	Drug(s)	P-Value	Fold Change (Group Means)	P-Value	Fold Change (Group Means)	P-Value	Fold Change (Group Means)	P-Value	Fold Change (Group Means)	P-Value	Fold Change (Group Means)
1418930_at		CXCL10	chemokine (C-X-C motif) ligand 10	Extracellular Space	cytokine	MDX-1100	6.96E-09	261.99	8.86E-02	1.17	1.93E-01	1.10	1.15E-04	6.45	3.78E-03	1.48
1436058_at		RSAD2	radical S-adenosyl methionine domain containing 2	Cytoplasm	enzyme		5.73E-06	60.51	4.81E-01	1.12	4.28E-01	1.13	2.16E-02	1.85	5.27E-01	1.12
1421578_at		CCL4	chemokine (C-C motif) ligand 4	Extracellular Space	cytokine		3.47E-07	59.21	6.73E-01	1.03	4.76E-01	1.05	2.74E-02	1.37	1.24E-01	1.13
1419561_at		CCL3L1/CCL3L3	chemokine (C-C motif) ligand 3-like 1	Extracellular Space	cytokine		4.99E-08	59.20	9.23E-01	1.01	5.69E-03	1.22	5.38E-05	1.84	2.49E-03	1.36
1449025_at		IFIT3	interferon-induced protein with tetratricopeptide repeats 3	Cytoplasm	other		9.53E-07	47.83	2.02E-01	1.12	2.25E-01	1.11	2.14E-02	1.72	4.41E-02	1.26
1418191_at		USP18	ubiquitin specific peptidase 18	Cytoplasm	peptidase		5.24E-07	44.57	2.51E-01	1.17	8.06E-02	1.14	1.01E-03	2.25	3.53E-02	1.23
1418293_at		IFIT2	interferon-induced protein with tetratricopeptide repeats 2	Cytoplasm	other		8.22E-07	43.86	4.24E-01	1.09	4.75E-01	1.09	4.08E-03	2.05	4.15E-02	1.28
1448728_a_at	Duplicate Gene Syn	NFKBIZ	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, zeta	Nucleus	transcription regulator		1.00E-07	38.33	6.55E-01	1.03	9.58E-01	1.00	2.51E-03	1.55	3.78E-01	0.96
1431591_s_at							3.15E-07	38.14	7.09E-01	1.04	7.28E-01	0.98	3.04E-03	1.85	1.30E-01	1.10
1451905_a_at		Mx1/Mx2	myxovirus (influenza virus) resistance 1	Nucleus	enzyme		8.78E-08	34.99	3.36E-01	1.07	3.60E-01	1.10	3.83E-04	1.89	3.75E-02	1.31
1417483_at	Duplicate Gene Syn	NFKBIZ	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, zeta	Nucleus	transcription regulator		5.88E-08	33.69	8.45E-01	1.01	7.26E-01	1.02	4.50E-05	2.53	1.57E-03	1.35
1419569_a_at		ISG20	interferon stimulated exonuclease gene 20kDa	Nucleus	enzyme		2.36E-08	33.56	4.90E-01	1.04	8.89E-01	1.00	2.36E-02	1.34	1.97E-01	1.07
1417601_at		RGS1	regulator of G-protein signaling 1	Plasma Membrane	other		1.49E-06	25.95	8.46E-01	0.98	7.09E-01	1.03	7.88E-03	1.47	9.97E-02	1.16
1420549_at		GBP2	guanylate binding protein 2, interferon-inducible	Nucleus	other		4.45E-07	23.03	8.27E-01	1.02	3.79E-01	0.96	1.35E-02	1.49	9.69E-01	1.00
1450826_a_at		Saa3	serum amyloid A 3	unknown	other		9.97E-07	22.96	8.90E-02	1.09	6.36E-01	0.95	4.09E-05	3.02	5.52E-02	1.17
1449399_a_at		IL1B	interleukin 1, beta	Extracellular Space	cytokine	IL-1 trap, canakinumab	2.17E-07	21.71	7.98E-01	1.02	2.67E-01	0.95	1.00E-04	3.25	1.26E-02	1.24
1424339_at		OASL	2'-5'-oligoadenylate synthetase-like	Cytoplasm	enzyme		1.23E-06	20.57	6.76E-02	1.10	9.38E-01	1.00	3.29E-02	1.35	4.76E-01	1.05
1460415_a_at	Duplicate Gene Syn	CD40	CD40 molecule, TNF receptor superfamily member 5	Plasma Membrane	transmembrane receptor	SGN-40 (anti-huCD40 mAb)	4.76E-08	18.35	9.36E-01	1.00	4.33E-01	0.98	3.50E-04	2.23	2.27E-01	1.05
1419004_s_at		BCL2A1	BCL2-related protein A1	Cytoplasm	other		2.64E-07	17.75	1.66E-01	1.09	7.42E-01	0.98	6.88E-04	2.41	1.55E-03	1.37
1424923_at		Serpina3g (includes	serine (or cysteine) peptidase inhibitor, clade A, member 3G	Extracellular Space	other		4.86E-08	17.66	3.57E-01	1.03	4.22E-01	0.98	3.42E-04	1.76	1.39E-01	1.07
1416111_at		CD83	CD83 molecule	Plasma Membrane	transmembrane receptor		6.16E-07	16.96	1.69E-01	1.09	7.39E-01	1.02	3.06E-05	3.11	6.58E-04	1.54
1419607_at		TNF	tumor necrosis factor	Extracellular Space	cytokine	adalimumab, etanercept, infliximab, CDP870, golimumab, thalidomide	1.45E-06	16.72	8.54E-01	0.99	6.45E-01	0.97	1.99E-03	1.65	7.05E-01	1.02
1423555_a_at		IFI44	interferon-induced protein 44	Cytoplasm	other		3.70E-07	16.55	4.28E-01	1.08	5.71E-01	1.05	1.23E-02	1.44	2.16E-01	1.10
1418126_at		CCL5	chemokine (C-C motif) ligand 5	Extracellular Space	cytokine		1.11E-07	16.07	6.82E-01	0.98	3.95E-01	0.96	2.26E-02	1.14	4.78E-01	0.98
1449473_s_at	Duplicate Gene Syn	CD40	CD40 molecule, TNF receptor superfamily member 5	Plasma Membrane	transmembrane receptor	SGN-40 (anti-huCD40 mAb)	2.64E-06	15.74	6.04E-01	0.97	8.06E-01	1.02	2.23E-04	2.28	9.88E-02	1.14
1421596_s_at	Duplicate Gene Syn	IFI44L	interferon-induced protein 44-like	unknown	other		2.30E-07	15.60	5.26E-01	0.94	8.46E-01	0.99	1.14E-03	1.35	1.59E-01	1.13
1418580_at		RTP4	receptor (chemosensory) transporter protein 4	Plasma Membrane	other		3.30E-06	15.56	4.65E-02	1.13	1.56E-01	1.11	2.78E-03	1.76	7.09E-02	1.12
1434380_at		GBP7	guanylate binding protein 7	Cytoplasm	enzyme		4.73E-07	15.49	1.28E-01	1.08	2.85E-01	1.03	3.94E-02	1.23	9.56E-01	0.99
1449009_at		Tgtp1/Tgtp2	T cell specific GTPase 1	unknown	enzyme		1.12E-06	15.40	7.24E-01	1.02	2.60E-01	1.06	8.07E-03	1.38	2.26E-01	1.07
1426774_at		PARP12	poly (ADP-ribose) polymerase family, member 12	Nucleus	other		8.55E-06	15.02	8.07E-02	1.24	3.21E-01	1.13	6.75E-02	1.27	1.31E-01	1.30
1425917_at	Duplicate Gene Syn	IFI44L	interferon-induced protein 44-like	unknown	other		1.04E-06	14.57	4.12E-01	1.06	6.26E-01	0.98	2.67E-03	1.29	2.38E-01	1.12
1450971_at	Duplicate Gene Syn	GADD45B	growth arrest and DNA-damage-inducible, beta	Cytoplasm	other		3.16E-07	14.33	7.94E-01	0.98	7.57E-01	0.99	1.32E-02	1.37	2.11E-01	0.94
1420591_at		GPR84	G protein-coupled receptor 84	Plasma Membrane	G-protein coupled receptor		6.10E-07	14.04	5.13E-01	0.95	9.65E-01	1.00	1.67E-03	3.39	3.88E-01	1.06
1449773_s_at	Duplicate Gene Syn	GADD45B	growth arrest and DNA-damage-inducible, beta	Cytoplasm	other		4.04E-06	13.90	8.96E-01	0.99	3.28E-01	1.09	7.03E-03	1.52	5.22E-01	1.07
1417244_a_at		IRF7	interferon regulatory factor 7	Nucleus	transcription regulator		1.05E-06	13.59	3.81E-01	1.05	4.19E-01	1.06	2.78E-02	1.33	8.96E-01	1.01
1417185_at		Ly6a (includes othe	lymphocyte antigen 6 complex, locus A	Plasma Membrane	other		3.75E-07	13.14	3.69E-01	0.97	8.43E-01	1.01	1.46E-01	1.12	1.22E-01	1.05
1417793_at		Irgm2	immunity-related GTPase family M member 2	Cytoplasm	enzyme		3.02E-06	13.08	6.83E-01	0.96	9.43E-01	0.99	2.86E-02	1.26	6.88E-01	1.05
1456212_x_at	Duplicate Gene Syn	SOCS3	suppressor of cytokine signaling 3	Cytoplasm	phosphatase		1.74E-07	13.00	6.87E-01	1.03	5.28E-01	1.05	3.97E-03	1.69	2.16E-01	1.17
1449363_at		ATF3	activating transcription factor 3	Nucleus	transcription regulator		2.46E-06	12.95	2.45E-01	0.94	9.05E-02	1.13	4.07E-03	1.39	4.44E-03	1.31
1418392_a_at		GBP4	guanylate binding protein 4	Cytoplasm	enzyme		7.07E-07	12.55	3.88E-01	1.03	7.96E-01	1.01	3.88E-03	1.40	6.15E-01	1.07
1426276_at		IFIH1	interferon induced with helicase C domain 1	Nucleus	enzyme		2.22E-07	12.40	2.49E-01	1.08	6.73E-01	0.98	1.74E-03	1.31	2.29E-01	1.08
1421551_s_at		Ifi202b	interferon activated gene 202B	Nucleus	other		3.93E-07	12.04	1.84E-01	1.11	5.64E-01	1.03	3.96E-03	1.36	8.52E-02	1.08
1451564_at		PARP14	poly (ADP-ribose) polymerase family, member 14	Cytoplasm	other		3.45E-06	11.88	1.95E-01	1.13	1.39E-01	1.16	4.25E-03	1.57	2.56E-02	1.27
1417141_at		Igtp	interferon gamma induced GTPase	Cytoplasm	enzyme		3.61E-07	11.84	9.43E-01	1.00	5.95E-01	1.02	6.31E-02	1.17	2.46E-01	0.95
1429947_a_at		ZBP1	Z-DNA binding protein 1	Cytoplasm	other		2.16E-06	11.74	2.33E-01	0.94	8.55E-01	1.01	5.08E-02	1.15	4.96E-01	0.96
1455899_x_at	Duplicate Gene Syn	SOCS3	suppressor of cytokine signaling 3	Cytoplasm	phosphatase		1.51E-06	11.54	9.46E-01	1.00	8.59E-01	1.02	9.97E-04	1.78	1.28E-01	1.12
1416576_at	Duplicate Gene Syn	SOCS3	suppressor of cytokine signaling 3	Cytoplasm	phosphatase		4.22E-07	10.77	6.54E-01	1.02	5.20E-01	1.03	1.70E-04	1.50	9.49E-01	1.00
1451426_at		DHX58	DEXH (Asp-Glu-X-His) box polypeptide 58	Cytoplasm	enzyme		3.87E-06	10.64	5.43E-01	1.05	3.19E-01	1.08	4.53E-02	1.23	5.82E-01	1.04
1449591_at		CASP4	caspase 4, apoptosis-related cysteine peptidase	Cytoplasm	peptidase		4.09E-07	10.14	3.60E-01	0.95	5.16E-01	0.95	3.73E-04	1.58	3.79E-01	0.96
1435331_at	Duplicate Gene Syn	Ifi204 (includes oth	interferon activated gene 204	Nucleus	transcription regulator		1.19E-07	9.79	9.33E-01	1.00	2.82E-01	0.93	1.04E-02	1.16	3.31E-01	1.07
1422006_at		EIF2AK2	eukaryotic translation initiation factor 2-alpha kinase 2	Cytoplasm	kinase		4.82E-07	9.49	6.53E-01	1.01	3.07E-01	0.95	1.05E-01	1.08	3.12E-01	1.03
1424775_at		OAS1	2'-5'-oligoadenylate synthetase 1, 40/46kDa	Cytoplasm	enzyme		3.14E-06	9.05	7.14E-01	1.02	2.37E-01	1.09	1.02E-02	1.22	3.71E-01	1.07
1435454_a_at		HELZ2	helicase with zinc finger 2, transcriptional coactivator	Nucleus	transcription regulator		3.16E-06	8.91	8.16E-01	1.02	5.23E-01	0.94	8.06E-03	1.37	1.56E-01	1.14
1450033_a_at	Duplicate Gene Syn	STAT1	signal transducer and activator of transcription 1, 91kDa	Nucleus	transcription regulator		3.45E-07	8.84	6.78E-01	1.03	1.75E-01	1.06	5.89E-03	1.30	4.63E-01	1.04
1420915_at	Duplicate Gene Syn	STAT1	signal transducer and activator of transcription 1, 91kDa	Nucleus	transcription regulator		2.78E-05	8.58	4.90E-01	1.05	4.47E-01	1.07	7.38E-03	1.24	1.44E-01	1.11
1427736_a_at		CCRL2	chemokine (C-C motif) receptor-like 2	Plasma Membrane	G-protein coupled receptor		2.35E-06	7.83	2.11E-01	1.08	1.33E-01	1.11	6.06E-04	1.93	1.95E-01	1.09
1418825_at		IRGM	immunity-related GTPase family, M	Cytoplasm	other		5.66E-07	7.77	1.31E-01	0.97	5.07E-02	1.05	5.12E-04	1.19	5.73E-01	0.98
1451860_a_at	Duplicate Gene Syn	Trim30a/Trim30d	tripartite motif-containing 30A	Cytoplasm	other		9.67E-07	7.76	6.55E-02	1.06	5.25E-02	1.11	2.17E-03	1.36	8.74E-03	1.17
1456494_a_at	Duplicate Gene Syn	Trim30a/Trim30d	tripartite motif-containing 30A	Cytoplasm	other		2.04E-06	7.60	7.72E-01	1.02	4.08E-01	0.94	5.91E-01	1.03	1.64E-01	0.89
1419192_at		Ifi41/Nup62-il4i1	interleukin 4 induced 1	Cytoplasm	enzyme		2.10E-06	7.58	1.42E-01	1.07	7.67E-01	0.98	1.92E-03	2.42	1.43E-04	1.37

							Stimulation Only		Compound Only				Stimulation and Compound			
			Probe Set Description				CpG vs. Medium		0.25 uM E6446 vs. Medium		1.25 uM E6446 vs. Medium		CpG + 0.25 uM E6446 vs. Medium		CpG + 1.25 uM E6446 vs. Medium	
1450034_at	Duplicate Gene Syn	STAT1	signal transducer and activator of transcription 1, 91kDa	Nucleus	transcription regulator		1.14E-06	7.43	8.56E-01	1.01	6.71E-01	0.98	6.57E-03	1.21	7.13E-01	1.02
1417292_at		Ifi47	interferon gamma inducible protein 47	Cytoplasm	other		2.92E-08	6.87	8.51E-01	1.00	6.71E-02	1.06	1.21E-02	1.15	5.69E-02	1.04
1425065_at		OAS2	2'-5'-oligoadenylate synthetase 2, 69/71kDa	Cytoplasm	enzyme		4.48E-07	6.79	3.86E-01	1.07	9.94E-01	1.00	1.07E-01	1.13	8.15E-01	0.99
1422953_at		FPR2	formyl peptide receptor 2	Plasma Membrane	G-protein coupled receptor		4.32E-06	6.71	9.34E-01	1.01	2.14E-01	0.91	6.51E-04	1.94	7.83E-01	0.98
1416897_at		PARP9	poly (ADP-ribose) polymerase family, member 9	Nucleus	other		1.63E-06	6.58	1.66E-01	1.08	2.76E-01	1.07	8.74E-03	1.20	6.16E-02	1.11
1426716_at		TDRD7	tudor domain containing 7	Cytoplasm	other		6.65E-06	6.56	8.32E-01	1.02	9.55E-01	1.00	1.19E-01	1.11	2.00E-01	1.09
1417300_at		SMPDL3B	sphingomyelin phosphodiesterase, acid-like 3B	Extracellular Space	enzyme		1.36E-07	6.54	2.70E-01	0.97	1.63E-02	0.91	4.39E-04	2.05	3.17E-01	1.08
1452178_at							1.79E-05	6.49	1.00E+00	1.00	6.56E-01	1.05	1.13E-01	1.19	3.02E-01	1.10
1427091_at		ZNFX1	zinc finger, NFX1-type containing 1	Nucleus	transcription regulator		8.79E-06	6.45	6.89E-01	1.03	7.39E-01	1.03	5.80E-02	1.18	2.64E-01	1.12
1420330_at	Duplicate Gene Syn	CLEC4E	C-type lectin domain family 4, member E	Plasma Membrane	other		2.97E-06	6.34	6.52E-02	1.15	2.63E-01	1.06	2.28E-05	2.90	4.67E-03	1.26
1420331_at	Duplicate Gene Syn	CLEC4E	C-type lectin domain family 4, member E	Plasma Membrane	other		1.19E-06	6.33	9.03E-01	0.99	1.98E-01	0.96	4.96E-06	2.42	6.90E-03	1.25
1449195_s_at	Duplicate Gene Syn	CXCL16	chemokine (C-X-C motif) ligand 16	Extracellular Space	cytokine		9.10E-06	6.31	4.00E-01	1.04	8.04E-01	0.98	4.69E-06	2.38	5.66E-04	1.26
1449317_at	Duplicate Gene Syn	CFLAR	CASP8 and FADD-like apoptosis regulator	Cytoplasm	other		3.63E-06	6.31	2.61E-01	0.92	4.13E-02	0.88	5.22E-02	1.17	6.36E-01	0.97
1419026_at		DAXX	death-domain associated protein	Nucleus	transcription regulator		1.47E-07	6.19	7.90E-01	1.01	9.43E-01	1.00	1.06E-01	1.11	6.53E-01	1.02
1448306_at	Duplicate Gene Syn	NFKBIA	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha	Cytoplasm	transcription regulator		1.71E-06	6.05	8.85E-01	0.99	1.44E-01	0.93	1.14E-04	2.62	9.54E-01	1.00
1448757_at		PML	promyelocytic leukemia	Nucleus	transcription regulator	arsenic trioxide	3.52E-07	6.02	8.09E-02	1.07	2.33E-01	1.09	2.19E-01	1.07	2.54E-01	1.05
1436172_at	Duplicate Gene Syn	Gm20559	predicted gene, 20559	unknown	other		2.11E-06	5.95	9.19E-02	1.08	4.07E-01	1.05	3.12E-02	1.19	3.45E-02	1.08
1416514_a_at		FSCN1	fascin homolog 1, actin-bundling protein (Strongylocentrotus purpuratus)	Cytoplasm	other		5.35E-06	5.84	9.49E-01	1.00	3.67E-01	0.93	3.60E-02	1.35	2.37E-01	1.16
1434484_at		1100001G20Rik	RIKEN cDNA 1100001G20 gene	Extracellular Space	other		2.18E-09	5.81	3.91E-01	0.96	1.54E-01	1.05	4.23E-03	1.20	1.21E-03	1.11
1451655_at		SLFN13	schlafen family member 13	Nucleus	enzyme		6.17E-07	5.67	5.81E-01	0.97	5.46E-01	0.97	1.46E-01	1.10	1.98E-01	0.95
1422924_at		Tnfsf9	tumor necrosis factor (ligand) superfamily, member 9	Plasma Membrane	other		1.12E-06	5.60	4.78E-01	0.97	6.91E-01	1.03	1.53E-03	1.55	2.42E-01	1.07
1436899_at		ZUFSP	zinc finger with UFM1-specific peptidase domain	unknown	other		6.93E-08	5.40	3.96E-03	1.09	1.75E-01	1.05	1.67E-03	1.15	1.13E-02	1.07
1421733_a_at		TPST1	tyrosylprotein sulfotransferase 1	Cytoplasm	enzyme		5.55E-06	5.32	5.33E-01	0.97	9.88E-01	1.00	9.14E-01	1.00	7.33E-01	1.02
1416010_a_at	Duplicate Gene Syn	EHD1	EH-domain containing 1	Cytoplasm	other		1.02E-06	5.17	3.04E-01	1.04	8.56E-01	0.99	1.51E-04	1.79	2.36E-02	1.15
1424617_at		Ifi35	interferon-induced protein 35	Nucleus	other		3.56E-06	5.15	5.57E-01	1.04	6.64E-01	1.02	1.35E-01	1.12	5.61E-01	0.97
1417961_a_at	Duplicate Gene Syn	Trim30a/Trim30d	tripartite motif-containing 30A	Cytoplasm	other		2.09E-06	5.13	7.41E-01	1.02	3.34E-01	0.95	7.09E-01	0.98	2.94E-02	0.84
1437226_x_at	Duplicate Gene Syn	MARCKSL1	MARCKS-like 1	Cytoplasm	other		6.37E-06	5.12	5.63E-01	0.97	2.88E-01	0.91	7.98E-04	1.79	4.74E-01	1.02
1423466_at		CCR7	chemokine (C-C motif) receptor 7	Plasma Membrane	G-protein coupled receptor		3.90E-07	5.11	6.52E-02	0.92	2.48E-02	0.93	1.46E-02	1.10	8.29E-02	0.97
1454169_a_at	Duplicate Gene Syn	Epsti1	epithelial stromal interaction 1 (breast)	unknown	other		5.35E-06	5.03	1.46E-01	0.93	8.22E-01	1.01	7.69E-02	1.18	5.77E-01	0.97
1427102_at		SLFN12L	schlafen family member 12-like	unknown	enzyme		4.16E-06	4.99	3.60E-02	1.15	6.69E-01	1.04	2.58E-01	1.16	4.68E-02	1.17
1449858_at	Duplicate Gene Syn	CD86	CD86 molecule	Plasma Membrane	transmembrane receptor	abatacept, belatacept	7.42E-07	4.96	1.30E-01	1.07	8.57E-01	1.00	1.82E-01	1.08	2.99E-01	1.03
1448175_at	Duplicate Gene Syn	EHD1	EH-domain containing 1	Cytoplasm	other		9.28E-07	4.95	7.28E-01	1.03	6.47E-01	0.98	5.17E-05	1.73	6.02E-01	1.03
1425686_at	Duplicate Gene Syn	CFLAR	CASP8 and FADD-like apoptosis regulator	Cytoplasm	other		1.22E-05	4.92	7.96E-01	1.02	2.88E-01	0.93	2.29E-01	1.12	8.18E-01	1.01
1422704_at		GK	glycerol kinase	Cytoplasm	kinase		4.28E-06	4.91	5.90E-01	1.02	4.02E-01	0.96	3.72E-03	1.27	3.55E-02	1.18
1421285_at		PIK3AP1	phosphoinositide-3-kinase adaptor protein 1	Cytoplasm	other		5.36E-06	4.90	6.43E-01	1.05	8.54E-01	1.02	1.42E-01	1.07	2.01E-01	1.07
1438855_x_at	Duplicate Gene Syn	TNFAIP2	tumor necrosis factor, alpha-induced protein 2	Extracellular Space	other		2.20E-05	4.86	8.46E-01	1.01	9.09E-01	1.01	5.13E-04	2.07	7.96E-02	1.18
1415922_s_at	Duplicate Gene Syn	MARCKSL1	MARCKS-like 1	Cytoplasm	other		1.51E-04	4.85	9.29E-01	0.99	7.34E-01	0.96	3.66E-03	1.87	7.46E-01	0.96
1423543_at		SWAP70	SWAP switching B-cell complex 70kDa subunit	Cytoplasm	other		1.45E-07	4.83	2.63E-01	1.05	7.13E-01	0.97	4.36E-04	1.20	1.04E-01	1.08
1421267_a_at	Duplicate Gene Syn	CITED2	Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 2	Nucleus	transcription regulator		1.12E-05	4.83	8.57E-01	1.01	7.86E-01	0.98	7.99E-01	0.99	8.16E-01	1.01
1417932_at		IL18	interleukin 18 (interferon-gamma-inducing factor)	Extracellular Space	cytokine		8.62E-06	4.82	8.65E-01	0.99	6.03E-01	0.97	3.03E-01	1.09	3.03E-01	0.97
1455581_x_at	Duplicate Gene Syn	Gm20559	predicted gene, 20559	unknown	other		2.96E-05	4.79	5.89E-01	1.04	7.77E-01	0.98	1.63E-01	1.16	4.48E-01	1.05
1417876_at		FCGR1A	Fc fragment of IgG, high affinity Ia, receptor (CD64)	Plasma Membrane	transmembrane receptor		1.16E-06	4.77	6.20E-01	1.01	9.57E-01	1.00	2.50E-01	0.97	8.19E-01	1.00
1449731_s_at	Duplicate Gene Syn	NFKBIA	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha	Cytoplasm	transcription regulator		2.29E-06	4.76	6.31E-01	0.97	5.66E-01	0.97	2.53E-04	2.43	4.66E-02	1.12
1424067_at		ICAM1	intercellular adhesion molecule 1	Plasma Membrane	transmembrane receptor		1.91E-06	4.76	6.85E-02	1.10	2.25E-01	1.07	4.63E-05	2.14	1.62E-01	1.07
1416011_x_at	Duplicate Gene Syn	EHD1	EH-domain containing 1	Cytoplasm	other		2.56E-07	4.74	9.60E-01	1.00	3.85E-01	0.95	2.05E-05	1.69	3.75E-01	1.07
1418718_at	Duplicate Gene Syn	CXCL16	chemokine (C-X-C motif) ligand 16	Extracellular Space	cytokine		2.73E-05	4.74	9.41E-01	1.00	5.73E-01	0.96	8.49E-04	1.79	3.56E-01	1.08
1420499_at		GCH1	GTP cyclohydrolase 1	Cytoplasm	enzyme		5.47E-06	4.73	2.91E-01	1.08	4.05E-01	1.06	1.77E-02	1.30	2.18E-01	1.08
1448380_at		LGALS3BP	lectin, galactoside-binding, soluble, 3 binding protein	Plasma Membrane	transmembrane receptor		2.14E-06	4.72	6.76E-01	1.02	6.82E-01	0.98	1.13E-01	1.08	7.78E-01	0.99
1416273_at	Duplicate Gene Syn	TNFAIP2	tumor necrosis factor, alpha-induced protein 2	Extracellular Space	other		5.85E-07	4.68	2.94E-01	1.06	1.25E-01	1.06	1.06E-04	1.88	2.34E-03	1.21
1418077_at	Duplicate Gene Syn	TRIM21	tripartite motif containing 21	Nucleus	enzyme		1.88E-07	4.67	5.02E-01	1.04	3.57E-01	1.03	1.61E-01	1.06	4.43E-04	1.07
1417409_at	Duplicate Gene Syn	JUN	jun proto-oncogene	Nucleus	transcription regulator		5.86E-06	4.66	7.07E-01	0.99	9.67E-01	1.00	2.86E-01	1.09	4.83E-01	1.03
1420697_at		SLC15A3	solute carrier family 15, member 3	Cytoplasm	transporter		2.10E-06	4.62	5.85E-01	0.98	9.96E-01	1.00	1.20E-02	1.37	4.86E-02	1.09
1424524_at		DRAM1	DNA-damage regulated autophagy modulator 1	Cytoplasm	other		1.76E-06	4.61	3.09E-01	0.96	7.09E-01	0.96	6.44E-05	1.49	2.22E-01	1.07
1448940_at	Duplicate Gene Syn	TRIM21	tripartite motif containing 21	Nucleus	enzyme		1.96E-05	4.60	7.28E-01	0.97	9.42E-01	1.00	8.98E-01	0.99	9.31E-01	0.99
1449222_at		EBI3	Epstein-Barr virus induced 3	Extracellular Space	cytokine		1.79E-06	4.60	3.42E-01	0.98	2.92E-01	0.96	4.37E-03	1.21	7.21E-01	0.99
1452087_at	Duplicate Gene Syn	Epsti1	epithelial stromal interaction 1 (breast)	unknown	other		4.80E-05	4.60	2.33E-01	0.91	5.04E-02	0.90	7.55E-02	1.09	5.59E-01	0.96
1450165_at		Sfn2	schlafen 2	Cytoplasm	other		5.74E-07	4.55	9.12E-01	1.00	8.18E-01	0.99	2.84E-03	1.36	1.43E-01	0.95
1424921_at		BST2	bone marrow stromal cell antigen 2	Plasma Membrane	other		7.97E-05	4.41	4.78E-01	0.93	3.52E-01	0.94	3.14E-01	1.07	6.28E-01	1.03
1451050_at		NT5C3A	5'-nucleotidase, cytosolic IIIA	Cytoplasm	phosphatase		5.30E-05	4.37	8.98E-01	0.99	6.12E-01	0.97	1.28E-01	1.07	1.20E-01	1.09
1428346_at		TRAFD1	TRAF-type zinc finger domain containing 1	unknown	other		7.31E-06	4.20	4.58E-01	1.04	7.50E-01	1.02	9.77E-02	1.10	2.27E-01	1.06
1425405_a_at		ADAR	adenosine deaminase, RNA-specific	Nucleus	enzyme		1.08E-07	4.20	5.52E-01	1.03	8.17E-01	1.01	7.81E-02	1.10	6.35E-01	1.02
1417190_at		NAMPT	nicotinamide phosphoribosyltransferase	Extracellular Space	cytokine		3.81E-07	4.19	6.55E-01	1.01	8.54E-02	1.05	1.70E-03	1.13	1.27E-02	1.10
1420888_at		BCL2L1	BCL2-like 1	Cytoplasm	other		1.42E-06	4.13	6.21E-01	1.02	7.72E-01	0.99	3.23E-01	0.95	5.14E-02	0.91
1416268_at		ETS2	v-ets erythroblastosis virus E26 oncogene homolog 2 (avian)	Nucleus	transcription regulator		8.23E-06	4.08	3.03E-01	0.94	1.51E-01	0.87	2.73E-02	1.19	6.02E-01	1.03
1452207_at	Duplicate Gene Syn	CITED2	Cbp/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 2	Nucleus	transcription regulator		3.78E-07	4.05	5.72E-01	0.98	2.31E-01	0.97	2.16E-01	0.97	8.47E-01	1.01
1420404_at	Duplicate Gene Syn	CD86	CD86 molecule	Plasma Membrane	transmembrane receptor	abatacept, belatacept	1.49E-05	4.05	1.99E-01	1.08	5.69E-01	0.97	1.63E-01	1.12	8.83E-01	1.01
1418635_at	Duplicate Gene Syn	ETV3	ets variant 3	Nucleus	transcription regulator		2.92E-07	3.97	2.94E-02	1.09	1.05E-01	1.10	3.22E-04	1.26	5.23E-03	1.11
1418401_a_at		DUSP16	dual specificity phosphatase 16	Nucleus	phosphatase		8.67E-06	3.96	9.48E-01	1.00	7.18E-01	1.03	5.43E-03	1.29	8.12E-02	1.13
1448694_at	Duplicate Gene Syn	JUN	jun proto-oncogene	Nucleus	transcription regulator		6.44E-07	3.87	3.76E-01	0.96	9.31E-01	1.01	8.57E-01	0.99	5.94E-02	1.09
1448958_at	Duplicate Gene Syn	TOR1AIP2	torsin A interacting protein 2	Cytoplasm	other		1.19E-06	3.84	9.07E-01	1.00	7.50E-02	0.92	1.85E-01	1.04	9.69E-01	1.00
1418637_at	Duplicate Gene Syn	ETV3	ets variant 3	Nucleus	transcription regulator		9.94E-06	3.84	4.09E-01	0.96	4.37E-01	0.96	3.66E-02	1.23	6.73E-02	1.15
1452676_a_at		PNPT1	polyribonucleotide nucleotidyltransferase 1	Cytoplasm	enzyme		3.38E-06	3.79	2.73E-01	0.95	6.19E-01	1.03	5.52E-01	1.04	8.54E-01	1.01
1424996_at	Duplicate Gene Syn	CFLAR	CASP8 and FADD-like apoptosis regulator	Cytoplasm	other		3.19E-07	3.78	6.72E-01	0.96	3.06E-01	0.95	3.59E-02	1.13	5.26E-01	1.03
1421098_at		STAP1	signal transducing adaptor family member 1	Cytoplasm	other		8.60E-06	3.74	4.26E-01	1.04	7.73E-01	0.98	1.42E-02	1.23	1.92E-01	1.09
1418133_at		BCL3	B-cell CLL/lymphoma 3	Nucleus	transcription regulator		4.77E-06	3.70	5.35E-01	1.02	4.20E-01	1.03	4.02E-04	1.65	1.12E-01	1.11
1435458_at	Duplicate Gene Syn	PIM1	pim-1 oncogene	Cytoplasm	kinase		3.60E-07	3.70	9.48E-01	1.00	6.29E-01	1.01	4.63E-04	1.35	1.89E-02	1.09
1425902_a_at		NFKB2	nuclear factor of kappa light polypeptide gene enhancer in B-cells 2 (p49/p100)	Nucleus	transcription regulator		5.87E-06	3.68	8.08E-01	1.01	7.59E-01	0.98	2.49E-04	1.63	4.77E-02	1.12

							Stimulation Only		Compound Only				Stimulation and Compound			
Probe Set Description							CpG vs. Medium		0.25 uM E6446 vs. Medium		1.25 uM E6446 vs. Medium		CpG + 0.25 uM E6446 vs. Medium		CpG + 1.25 uM E6446 vs. Medium	
1435526_at	Duplicate Gene Syn	TOR1AIP2	torsin A interacting protein 2	Cytoplasm	other		1.79E-04	3.64	4.77E-01	1.08	6.44E-01	1.05	4.75E-01	1.09	3.27E-01	1.14
1425406_at	Duplicate Gene Syn	CLEC4A	C-type lectin domain family 4, member A	Plasma Membrane	transmembrane receptor		1.81E-05	3.62	5.95E-01	0.97	2.45E-01	0.90	2.18E-01	1.09	7.13E-02	0.87
1419482_at	Duplicate Gene Syn	C3AR1	complement component 3a receptor 1	Plasma Membrane	G-protein coupled receptor		3.94E-04	3.62	6.26E-01	1.06	9.40E-01	0.99	1.93E-01	1.21	8.68E-01	1.02
1452653_at		SLC25A22	solute carrier family 25 (mitochondrial carrier: glutamate), member 22	Cytoplasm	transporter		2.63E-05	3.60	4.36E-01	1.04	9.65E-01	1.00	5.84E-01	1.02	6.09E-01	0.98
1422141_s_at							3.96E-07	3.59	9.94E-01	1.00	1.26E-03	0.88	6.03E-01	0.98	9.10E-01	1.00
1423954_at		C3	complement component 3	Extracellular Space	peptidase		1.65E-08	3.51	1.41E-01	1.08	1.81E-01	0.97	4.36E-04	1.55	2.17E-02	1.14
1426133_a_at		MITD1	MIT, microtubule interacting and transport, domain containing 1	unknown	other		1.41E-05	3.51	4.33E-01	1.07	2.37E-01	1.06	1.88E-01	1.08	7.13E-02	1.12
1426112_a_at		CD72	CD72 molecule	Plasma Membrane	transmembrane receptor		1.18E-06	3.45	4.64E-02	1.05	9.83E-01	1.00	5.96E-02	1.10	1.61E-01	1.04
1448775_at	Duplicate Gene Syn	Ifi204 (includes oth	interferon activated gene 204	Nucleus	transcription regulator		5.12E-06	3.44	9.33E-01	1.00	4.85E-01	1.03	1.61E-01	1.07	5.02E-01	1.03
1451567_a_at	Duplicate Gene Syn	Ifi204 (includes oth	interferon activated gene 204	Nucleus	transcription regulator		1.80E-06	3.40	7.42E-01	0.99	8.04E-01	0.99	8.66E-01	1.01	6.37E-01	1.02
1425719_a_at		NMI	N-myc (and STAT) interactor	Cytoplasm	transcription regulator		5.12E-06	3.39	2.97E-01	1.02	8.99E-01	1.00	4.12E-02	1.10	1.37E-02	1.11
1420671_x_at	Duplicate Gene Syn	Ms4a4b (includes o	membrane-spanning 4-domains, subfamily A, member 4B	Plasma Membrane	other		1.15E-08	3.37	2.37E-01	1.04	5.91E-03	0.97	2.38E-02	1.12	4.03E-02	1.03
1427511_at							2.38E-07	3.37	7.90E-01	1.02	3.19E-01	1.08	1.67E-04	1.37	3.46E-02	1.09
1423006_at	Duplicate Gene Syn	PIM1	pim-1 oncogene	Cytoplasm	kinase		1.13E-05	3.36	5.38E-01	0.97	7.56E-01	0.98	7.15E-03	1.23	6.39E-01	0.97
1416016_at		TAP1	transporter 1, ATP-binding cassette, sub-family B (MDR/TAP)	Cytoplasm	transporter		1.65E-05	3.36	3.63E-01	1.05	3.59E-01	1.06	5.80E-02	1.17	2.38E-01	1.07
1435792_at		Csprs (includes oth	component of Sp100-rs	Plasma Membrane	G-protein coupled receptor		2.24E-06	3.35	2.01E-01	1.05	4.12E-01	1.04	4.28E-01	1.05	1.16E-01	1.12
1451160_s_at		Pvr	poliovirus receptor	Plasma Membrane	other		5.09E-06	3.34	8.69E-02	1.06	5.65E-01	0.99	4.44E-03	1.15	3.88E-01	1.04
1418115_s_at	Duplicate Gene Syn	TOR1AIP2	torsin A interacting protein 2	Cytoplasm	other		3.35E-07	3.34	7.39E-01	0.99	2.38E-01	0.97	2.42E-01	1.04	6.36E-01	0.99
1452925_a_at	Duplicate Gene Syn	MARCH5	membrane-associated ring finger (C3HC4) 5	Cytoplasm	enzyme		2.77E-06	3.33	8.11E-01	1.01	1.32E-01	1.05	6.50E-02	1.11	4.26E-01	1.03
1424638_at	Duplicate Gene Syn	CDKN1A	cyclin-dependent kinase inhibitor 1A (p21, Cip1)	Nucleus	kinase		5.37E-07	3.33	3.90E-01	0.97	1.79E-01	1.04	6.74E-03	1.26	1.78E-01	0.95
1449049_at		TLR1	toll-like receptor 1	Plasma Membrane	transmembrane receptor		6.80E-06	3.31	2.46E-01	0.94	1.83E-01	0.91	2.55E-01	1.04	2.97E-01	1.07
1448325_at		PPP1R15A	protein phosphatase 1, regulatory subunit 15A	Cytoplasm	other		2.77E-07	3.28	6.88E-01	0.98	5.81E-01	0.98	1.38E-02	1.24	8.23E-01	0.99
1449455_at		HCK	hemopoietic cell kinase	Cytoplasm	kinase	bosutinib	6.75E-07	3.25	8.68E-01	0.99	7.18E-02	0.94	3.30E-04	1.35	9.95E-01	1.00
1435415_x_at	Duplicate Gene Syn	MARCKSL1	MARCKS-like 1	Cytoplasm	other		5.61E-07	3.24	3.92E-01	1.04	9.37E-01	1.01	5.20E-05	1.67	1.27E-01	1.07
1418116_at	Duplicate Gene Syn	TOR1AIP2	torsin A interacting protein 2	Cytoplasm	other		2.77E-06	3.24	9.31E-02	1.07	8.52E-01	0.99	1.67E-01	1.06	8.81E-01	1.01
1423467_at	Duplicate Gene Syn	Ms4a4b (includes o	membrane-spanning 4-domains, subfamily A, member 4B	Plasma Membrane	other		6.16E-06	3.22	4.94E-01	1.03	8.23E-02	0.92	9.06E-01	1.00	2.91E-01	0.93
1415972_at	Duplicate Gene Syn	MARCKS	myristoylated alanine-rich protein kinase C substrate	Plasma Membrane	other		5.50E-04	3.22	3.14E-01	1.12	9.51E-01	1.01	2.24E-01	1.18	6.54E-02	1.30
1415971_at	Duplicate Gene Syn	MARCKS	myristoylated alanine-rich protein kinase C substrate	Plasma Membrane	other		9.58E-07	3.20	7.23E-01	1.02	6.12E-01	0.99	7.34E-03	1.08	3.12E-01	1.06
1421679_a_at	Duplicate Gene Syn	CDKN1A	cyclin-dependent kinase inhibitor 1A (p21, Cip1)	Nucleus	kinase		7.94E-06	3.20	2.07E-01	0.86	1.06E-01	0.91	2.61E-02	1.18	1.33E-02	0.85
1417371_at	Duplicate Gene Syn	PELI1	pellino E3 ubiquitin protein ligase 1	Cytoplasm	enzyme		4.84E-06	3.19	3.26E-01	1.05	2.10E-01	1.06	2.19E-02	1.14	1.44E-01	1.06
1435627_x_at	Duplicate Gene Syn	MARCKSL1	MARCKS-like 1	Cytoplasm	other		2.75E-06	3.15	8.00E-01	1.01	7.81E-01	0.99	1.17E-03	1.50	8.03E-01	1.01
1416239_at		ASS1	argininosuccinate synthase 1	Cytoplasm	enzyme		9.72E-07	3.13	4.33E-01	1.06	7.68E-01	1.00	7.85E-04	1.15	1.18E-03	1.09
1448830_at		DUSP1	dual specificity phosphatase 1	Nucleus	phosphatase		1.10E-05	3.10	6.85E-03	0.89	5.02E-03	0.83	6.09E-03	1.24	7.65E-03	0.80
1428838_a_at	Duplicate Gene Syn	DCK	deoxycytidine kinase	Nucleus	kinase	fludarabine phosphate, cladribine	8.56E-05	3.07	6.82E-01	0.96	3.95E-01	0.91	4.51E-01	0.95	2.83E-01	0.90
1419315_at		SLAMF9	SLAM family member 9	Extracellular Space	other		1.53E-05	3.06	2.34E-01	1.04	3.43E-01	0.96	1.03E-03	1.31	5.21E-01	1.03
1419483_at	Duplicate Gene Syn	C3AR1	complement component 3a receptor 1	Plasma Membrane	G-protein coupled receptor		2.32E-05	3.05	5.33E-01	1.05	9.32E-01	1.01	2.95E-01	1.10	8.17E-01	0.99
1431843_a_at		NFKBIE	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, epsilon	Nucleus	transcription regulator		1.89E-05	3.05	7.93E-01	1.02	2.88E-01	0.94	5.44E-04	1.95	1.30E-01	1.12
1419212_at		ICOSLG	inducible T-cell co-stimulator ligand	Plasma Membrane	other		1.52E-04	3.05	3.89E-01	1.05	4.75E-01	0.96	2.04E-03	1.50	1.72E-01	1.10
1450698_at		DUSP2	dual specificity phosphatase 2	Nucleus	phosphatase		3.65E-08	3.04	1.66E-02	0.95	9.54E-01	1.00	8.71E-04	1.46	3.26E-03	1.09
1419135_at		LTB	lymphotoxin beta (TNF superfamily, member 3)	Extracellular Space	cytokine		8.63E-05	3.02	5.80E-01	1.06	2.18E-01	1.10	8.86E-04	1.75	1.20E-01	1.13
1424754_at		MS4A7	membrane-spanning 4-domains, subfamily A, member 7	unknown	other		3.80E-05	2.99	4.71E-01	1.07	3.52E-01	1.06	5.83E-01	1.05	3.03E-01	1.07
1432478_a_at	Duplicate Gene Syn	RNF19B	ring finger protein 19B	unknown	other		4.43E-06	2.99	5.98E-01	0.98	2.72E-01	0.95	7.78E-04	1.62	1.04E-01	1.15
1416505_at		NR4A1	nuclear receptor subfamily 4, group A, member 1	Nucleus	ligand-dependent nuclear receptor		3.70E-05	2.97	1.10E-01	1.10	4.43E-02	1.06	1.16E-03	1.31	7.05E-04	1.19
1450291_s_at	Duplicate Gene Syn	Ms4a4b (includes o	membrane-spanning 4-domains, subfamily A, member 4B	Plasma Membrane	other		6.68E-06	2.96	9.08E-01	1.00	4.81E-01	0.97	3.02E-02	1.11	5.27E-01	1.02
1421392_a_at		BIRC3	baculoviral IAP repeat containing 3	Cytoplasm	enzyme		1.22E-05	2.95	8.47E-01	0.99	9.84E-01	1.00	7.87E-04	1.49	1.38E-01	1.07
1417372_a_at	Duplicate Gene Syn	PELI1	pellino E3 ubiquitin protein ligase 1	Cytoplasm	enzyme		2.31E-05	2.95	9.84E-01	1.00	1.07E-01	0.92	1.41E-01	1.09	7.89E-01	1.03
1426971_at	Duplicate Gene Syn	UBA7	ubiquitin-like modifier activating enzyme 7	Cytoplasm	enzyme		1.75E-06	2.93	3.40E-01	0.93	3.71E-01	0.93	6.55E-01	1.04	1.28E-01	1.04
1454633_at	Duplicate Gene Syn	ETNK1	ethanolamine kinase 1	Cytoplasm	kinase		1.15E-04	2.93	8.45E-01	0.99	6.92E-01	0.98	9.13E-01	0.99	3.29E-01	1.05
1450495_a_at		KLRC4-KLRK1/KLRK	killer cell lectin-like receptor subfamily K, member 1	Plasma Membrane	transmembrane receptor		1.42E-04	2.89	5.75E-01	0.97	5.29E-01	1.03	4.24E-01	1.04	8.94E-01	0.99
1453299_a_at	Duplicate Gene Syn	PNP	purine nucleoside phosphorylase	Nucleus	enzyme	forodesine, 9-deaza-9-(3-thienylmethyl) guanine	4.82E-07	2.89	4.15E-01	0.99	9.22E-01	1.00	9.92E-02	1.02	6.51E-02	1.04
1421854_at	Duplicate Gene Syn	FGL2	fibrinogen-like 2	Extracellular Space	peptidase		1.29E-05	2.88	9.23E-01	1.00	6.00E-01	0.98	1.72E-02	0.77	3.13E-01	0.94
1422013_at	Duplicate Gene Syn	CLEC4A	C-type lectin domain family 4, member A	Plasma Membrane	transmembrane receptor		1.92E-05	2.86	5.17E-01	1.03	4.98E-01	0.97	1.63E-02	1.16	8.07E-01	0.99
1448171_at		SIAH2	siah E3 ubiquitin protein ligase 2	Nucleus	transcription regulator		6.18E-06	2.82	8.59E-02	0.91	4.36E-01	0.97	5.78E-03	1.26	1.41E-01	0.94
1428843_at	Duplicate Gene Syn	MARCH5	membrane-associated ring finger (C3HC4) 5	Cytoplasm	enzyme		1.66E-07	2.82	4.22E-01	0.98	6.61E-01	0.99	4.13E-03	1.06	8.05E-01	1.01
1425603_at		TMEM176A	transmembrane protein 176A	unknown	other		2.22E-05	2.81	1.03E-01	1.07	7.05E-01	0.99	5.93E-04	1.41	1.86E-01	1.09
1422512_a_at	Duplicate Gene Syn	OGFR	opioid growth factor receptor	Plasma Membrane	other	enkephalin, methionine	3.47E-05	2.80	8.14E-01	0.98	8.00E-01	1.03	3.33E-01	1.07	5.35E-01	1.04
1417523_at	Duplicate Gene Syn	PLEK	pleckstrin	Cytoplasm	other		1.12E-05	2.79	8.31E-01	1.01	2.33E-01	1.06	2.76E-03	1.30	4.20E-02	1.15
1453181_x_at	Duplicate Gene Syn	PLSCR1	phospholipid scramblase 1	Plasma Membrane	enzyme		3.69E-06	2.78	7.37E-01	1.02	2.37E-02	1.06	5.54E-02	1.11	2.26E-03	1.15
1415899_at		JUNB	jun B proto-oncogene	Nucleus	transcription regulator		1.35E-05	2.77	2.43E-01	0.93	3.67E-01	0.93	9.39E-05	1.65	7.61E-01	1.01
1433514_at	Duplicate Gene Syn	ETNK1	ethanolamine kinase 1	Cytoplasm	kinase		6.07E-06	2.77	9.12E-01	1.00	5.12E-01	0.98	4.20E-01	1.04	3.75E-02	1.11
1450672_a_at		TREX1	three prime repair exonuclease 1	Nucleus	enzyme		2.12E-05	2.77	7.09E-01	0.98	9.40E-01	1.00	1.26E-02	1.20	3.42E-01	0.95
1451122_at	Duplicate Gene Syn	IDI1	isopentenyl-diphosphate delta isomerase 1	Cytoplasm	enzyme		2.40E-05	2.76	6.21E-02	1.14	3.77E-03	1.31	1.50E-03	1.44	1.67E-03	1.51
1451082_at	Duplicate Gene Syn	FTSJD2	Ftsj methyltransferase domain containing 2	unknown	enzyme		1.01E-05	2.75	8.63E-01	1.01	5.72E-01	0.96	4.01E-01	1.04	7.00E-01	1.02
1426970_a_at	Duplicate Gene Syn	UBA7	ubiquitin-like modifier activating enzyme 7	Cytoplasm	enzyme		1.16E-05	2.74	1.14E-01	0.96	3.41E-01	0.96	6.22E-01	0.98	2.36E-01	1.03
1420088_at	Duplicate Gene Syn	NFKBIA	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha	Cytoplasm	transcription regulator		9.21E-07	2.74	8.84E-01	1.00	2.66E-01	0.97	5.57E-05	1.88	7.09E-02	1.07
1422959_s_at	Duplicate Gene Syn	RNF114	ring finger protein 114	Extracellular Space	other		1.83E-05	2.73	9.85E-01	1.00	7.74E-01	0.98	1.71E-01	1.09	7.37E-01	0.98
1429527_a_at	Duplicate Gene Syn	PLSCR1	phospholipid scramblase 1	Plasma Membrane	enzyme		1.29E-05	2.72	3.73E-01	1.04	5.51E-01	1.02	5.05E-01	1.05	6.29E-01	1.04
1435226_at	Duplicate Gene Syn	RNF19B	ring finger protein 19B	unknown	other		1.42E-05	2.69	7.96E-01	0.99	1.19E-01	1.04	4.62E-05	1.53	2.01E-02	1.14
1417193_at	Duplicate Gene Syn	SOD2	superoxide dismutase 2, mitochondrial	Cytoplasm	enzyme		2.72E-06	2.69	8.61E-01	1.01	3.78E-01	1.02	5.84E-03	1.25	7.81E-02	1.07
1420618_at		CPEB4	cytoplasmic polyadenylation element binding protein 4	Plasma Membrane	other		5.71E-04	2.68	5.64E-01	1.05	8.21E-01	0.98	1.69E-01	1.20	1.52E-01	1.24
1448610_a_at	Duplicate Gene Syn	SOD2	superoxide dismutase 2, mitochondrial	Cytoplasm	enzyme		5.61E-07	2.68	2.90E-01	1.02	2.79E-01	1.03	2.56E-03	1.26	5.81E-02	1.07
1421217_a_at		LGALS9	lectin, galactoside-binding, soluble, 9	Extracellular Space	other		4.54E-06	2.65	4.30E-01	1.05	2.80E-01	1.06	4.73E-02	1.05	2.64E-01	1.03
1427689_a_at		TNIP1	TNFAIP3 interacting protein 1	Nucleus	other		5.63E-06	2.65	4.01E-01	1.01	2.39E-01	0.94	1.93E-05	1.62	8.54E-01	1.01

							Stimulation Only		Compound Only				Stimulation and Compound			
		Probe Set Description					CpG vs. Medium		0.25 uM E6446 vs. Medium		1.25 uM E6446 vs. Medium		CpG + 0.25 uM E6446 vs. Medium		CpG + 1.25 uM E6446 vs. Medium	
1426903_at		FNDC3A	fibronectin type III domain containing 3A	Cytoplasm	other		1.10E-04	2.58	8.97E-01	0.99	4.29E-01	0.95	5.29E-01	1.05	2.90E-01	1.09
1419598_at	Duplicate Gene Syn	MS4A6A	membrane-spanning 4-domains, subfamily A, member 6A	unknown	other		1.31E-04	2.58	2.67E-01	1.06	5.76E-01	0.98	9.43E-01	1.00	9.87E-02	1.10
1419599_s_at	Duplicate Gene Syn	MS4A6A	membrane-spanning 4-domains, subfamily A, member 6A	unknown	other		7.35E-06	2.57	6.20E-01	1.02	4.10E-01	0.97	6.43E-01	0.98	3.57E-01	1.03
1423161_s_at	Duplicate Gene Syn	SPRED1	sprouty-related, EVH1 domain containing 1	Plasma Membrane	other		7.68E-05	2.57	5.55E-01	0.95	6.28E-01	0.98	4.84E-01	1.08	7.39E-01	1.02
1423681_at	Duplicate Gene Syn	FTSJD2	FtsJ methyltransferase domain containing 2	unknown	enzyme		8.37E-05	2.57	5.63E-01	0.96	8.48E-01	0.98	2.78E-01	1.08	4.20E-01	1.06
1425193_at	Duplicate Gene Syn	SPPL2A	signal peptide peptidase like 2A	Plasma Membrane	peptidase		5.03E-05	2.56	7.46E-01	1.02	5.06E-01	0.96	6.19E-02	1.11	8.51E-01	1.01
1418901_at		CEBPB	CCAAT/enhancer binding protein (C/EBP), beta	Nucleus	transcription regulator		1.94E-04	2.56	8.30E-01	0.99	9.50E-01	0.99	3.13E-04	1.71	5.93E-01	0.98
1448939_at		USP25	ubiquitin specific peptidase 25	unknown	peptidase		3.66E-05	2.56	3.84E-01	0.94	1.04E-01	0.90	8.20E-01	0.97	5.68E-01	0.93
1448436_a_at		IRF1	interferon regulatory factor 1	Nucleus	transcription regulator		6.65E-07	2.56	8.87E-01	1.00	1.36E-02	1.09	5.89E-02	1.08	3.71E-02	1.04
1455229_x_at	Duplicate Gene Syn	PGS1	phosphatidylglycerophosphate synthase 1	Cytoplasm	enzyme		1.67E-05	2.55	2.68E-01	0.94	9.42E-01	1.00	3.46E-01	1.06	6.21E-01	1.02
1421685_at		Clec4b1	C-type lectin domain family 4, member b1	Plasma Membrane	other		3.67E-05	2.55	5.43E-01	1.04	2.24E-01	0.91	1.13E-02	1.28	7.78E-02	1.09
1427874_at	Duplicate Gene Syn	RNF114	ring finger protein 114	Extracellular Space	other		1.32E-07	2.54	9.21E-01	1.00	2.27E-01	0.97	1.47E-01	1.09	9.22E-01	1.01
1428572_at		BASP1	brain abundant, membrane attached signal protein 1	Nucleus	transcription regulator		1.77E-05	2.54	2.44E-01	1.04	3.71E-02	1.07	1.11E-03	1.26	2.94E-03	1.14
1418536_at	Duplicate Gene Syn	HLA-B	major histocompatibility complex, class I, B	Plasma Membrane	transmembrane receptor		2.43E-05	2.54	8.98E-01	1.01	8.19E-01	0.99	1.64E-02	1.20	6.38E-01	1.02
1423401_at		ETV6	ets variant 6	Nucleus	transcription regulator		2.72E-04	2.53	7.19E-01	1.04	9.10E-01	0.99	2.18E-01	1.12	3.95E-01	1.09
1423870_at		AIDA	axin interactor, dorsalization associated	Cytoplasm	other		8.15E-07	2.52	6.58E-01	1.01	7.66E-01	1.01	5.40E-01	1.02	6.15E-01	0.99
1415973_at	Duplicate Gene Syn	MARCKS	myristoylated alanine-rich protein kinase C substrate	Plasma Membrane	other		3.84E-05	2.52	8.03E-01	0.99	2.01E-01	0.96	5.54E-01	1.04	4.15E-01	1.03
1425407_s_at	Duplicate Gene Syn	CLEC4A	C-type lectin domain family 4, member A	Plasma Membrane	transmembrane receptor		1.08E-05	2.51	6.64E-02	1.09	4.65E-01	0.98	3.93E-02	1.15	2.73E-01	0.97
1454046_x_at	Duplicate Gene Syn	PGS1	phosphatidylglycerophosphate synthase 1	Cytoplasm	enzyme		1.06E-05	2.51	1.63E-01	0.95	8.90E-01	1.01	4.48E-01	1.02	4.91E-01	1.02
1449176_a_at	Duplicate Gene Syn	DCK	deoxycytidine kinase	Nucleus	kinase	fludarabine phosphate, cladribine	1.65E-05	2.51	1.15E-01	1.06	4.02E-01	0.96	5.08E-01	0.95	5.35E-01	1.03
1456028_x_at	Duplicate Gene Syn	MARCKS	myristoylated alanine-rich protein kinase C substrate	Plasma Membrane	other		4.15E-04	2.51	3.13E-01	1.09	7.77E-01	1.03	1.86E-01	1.14	3.88E-01	1.14
1416530_a_at	Duplicate Gene Syn	PNP	purine nucleoside phosphorylase	Nucleus	enzyme	forodesine, 9-deaza-9-(3-thienylmethyl) guanine	1.96E-06	2.51	3.62E-01	1.02	3.79E-01	1.02	2.38E-01	1.03	1.12E-01	1.07
1421322_a_at		IRF9	interferon regulatory factor 9	Nucleus	transcription regulator		2.21E-06	2.49	1.15E-01	1.05	2.81E-01	1.02	4.29E-03	1.09	2.19E-02	0.95
1419410_at		BATF	basic leucine zipper transcription factor, ATF-like	Nucleus	transcription regulator		8.24E-06	2.46	4.39E-01	0.97	8.81E-01	1.01	2.70E-02	1.12	3.23E-01	1.03
1418154_at		N4BP1	NEDD4 binding protein 1	Cytoplasm	other		2.72E-05	2.45	7.36E-01	0.99	5.57E-01	0.97	1.13E-02	1.22	2.39E-01	1.06
1451593_at	Duplicate Gene Syn	HLA-B	major histocompatibility complex, class I, B	Plasma Membrane	transmembrane receptor		4.26E-06	2.45	1.89E-02	1.07	2.41E-02	1.07	3.43E-03	1.31	7.29E-03	1.11
1420394_s_at		Gp49a/Lilrb4	leukocyte immunoglobulin-like receptor, subfamily B, member 4	unknown	other		1.67E-06	2.45	2.86E-02	1.14	8.99E-03	1.11	4.54E-05	1.44	4.01E-04	1.31
1454045_a_at	Duplicate Gene Syn	PGS1	phosphatidylglycerophosphate synthase 1	Cytoplasm	enzyme		1.76E-06	2.44	1.02E-01	0.96	4.79E-02	0.96	3.58E-01	1.04	9.48E-01	1.00
1426084_a_at		Tor1aip1	torsin A interacting protein 1	Nucleus	other		6.21E-07	2.44	9.15E-02	0.94	2.69E-02	0.98	2.63E-01	1.01	1.01E-01	0.95
1424929_a_at		TRIM26	tripartite motif containing 26	Cytoplasm	other		4.76E-05	2.44	6.06E-01	0.97	9.50E-01	0.99	5.55E-01	1.04	3.97E-01	1.06
1448749_at	Duplicate Gene Syn	PLEK	pleckstrin	Cytoplasm	other		5.42E-05	2.44	5.20E-01	1.04	1.58E-01	1.08	1.29E-03	1.35	1.69E-02	1.16
1451821_a_at		Sp100	nuclear antigen Sp100	Nucleus	transcription regulator		4.98E-06	2.43	8.67E-02	1.06	1.41E-01	1.05	4.00E-01	0.98	1.09E-01	1.05
1448106_at		NECAP1	NECAP endocytosis associated 1	Plasma Membrane	other		9.21E-06	2.43	3.51E-01	1.03	6.88E-01	0.98	2.63E-02	1.10	3.03E-01	1.04
1450459_at	Duplicate Gene Syn	SPPL2A	signal peptide peptidase like 2A	Plasma Membrane	peptidase		9.48E-05	2.43	5.80E-01	0.95	7.34E-01	0.96	3.90E-01	1.07	2.67E-01	0.91
1421855_at	Duplicate Gene Syn	FGL2	fibrinogen-like 2	Extracellular Space	peptidase		3.65E-05	2.41	5.53E-01	1.03	3.76E-01	0.96	4.43E-02	0.79	8.77E-01	0.99
1423160_at	Duplicate Gene Syn	SPRED1	sprouty-related, EVH1 domain containing 1	Plasma Membrane	other		5.00E-05	2.40	7.19E-01	0.98	5.46E-01	0.96	4.31E-01	1.06	8.57E-01	0.99
1452414_s_at	Duplicate Gene Syn	CCDC86	coiled-coil domain containing 86	Nucleus	other		7.40E-05	2.40	3.88E-01	0.94	4.70E-01	0.96	1.22E-01	1.13	3.09E-01	1.07
1435133_at		UGCG	UDP-glucose ceramide glucosyltransferase	Cytoplasm	enzyme	N-butyldeoxygalactonojirimycin, N-butyldeoxynojirimycin	3.17E-05	2.39	5.09E-01	1.06	3.41E-01	1.06	2.61E-01	1.09	2.45E-02	1.22
1429884_at		SRGAP2	SLIT-ROBO Rho GTPase activating protein 2	Cytoplasm	other		1.98E-06	2.39	4.50E-01	0.97	7.36E-01	0.98	8.89E-01	0.99	6.30E-01	1.02
1419595_a_at		GGH	gamma-glutamyl hydrolase (conjugase, folylpolygammaglutamyl hydrolase)	Cytoplasm	peptidase		6.68E-05	2.38	7.32E-01	1.02	8.42E-02	0.92	5.48E-03	1.21	1.52E-02	1.09
1439012_a_at	Duplicate Gene Syn	DCK	deoxycytidine kinase	Nucleus	kinase	fludarabine phosphate, cladribine	6.20E-04	2.38	6.28E-01	1.02	3.37E-01	1.04	7.42E-01	0.97	4.11E-01	1.07
1448328_at		SH3BP2	SH3-domain binding protein 2	Cytoplasm	other		1.84E-04	2.37	5.24E-01	1.05	6.72E-01	1.04	1.01E-01	1.17	1.67E-01	1.16
1452117_a_at		FYB	FYN binding protein	Nucleus	other		3.46E-07	2.35	1.76E-01	1.06	3.82E-01	0.98	3.99E-04	1.32	3.14E-03	1.13
1435872_at							3.14E-04	2.35	9.70E-01	1.00	8.96E-01	1.01	6.02E-02	1.17	3.47E-01	1.08
1450506_a_at		AEN	apoptosis enhancing nuclease	Nucleus	enzyme		1.27E-05	2.34	9.60E-01	1.00	4.84E-01	1.06	9.81E-02	1.10	8.40E-02	1.09
1423214_at		PLXNC1	plexin C1	Plasma Membrane	transmembrane receptor		5.18E-05	2.34	9.38E-01	0.99	4.63E-01	0.98	6.09E-01	1.03	3.67E-01	1.07
1415713_a_at		DDX24	DEAD (Asp-Glu-Ala-Asp) box polypeptide 24	Nucleus	enzyme		9.37E-06	2.34	3.81E-01	1.03	7.47E-01	1.02	9.37E-02	1.07	1.68E-01	1.07
1456700_x_at	Duplicate Gene Syn	MARCKS	myristoylated alanine-rich protein kinase C substrate	Plasma Membrane	other		1.62E-04	2.33	1.44E-01	0.94	1.16E-01	0.94	3.66E-01	0.95	5.00E-01	1.05
1425974_a_at	Duplicate Gene Syn	TRIM25	tripartite motif containing 25	Cytoplasm	transcription regulator		4.90E-05	2.32	4.16E-01	1.04	8.47E-01	1.01	2.63E-01	1.06	5.05E-02	1.14
1423392_at	Duplicate Gene Syn	CLIC4	chloride intracellular channel 4	Plasma Membrane	ion channel		2.46E-06	2.32	8.06E-01	1.01	1.43E-01	0.95	5.12E-01	1.03	2.41E-02	0.96
1422978_at		CYBB	cytochrome b-245, beta polypeptide	Cytoplasm	enzyme		4.73E-04	2.32	6.64E-01	0.96	4.01E-01	0.91	1.68E-02	1.39	6.48E-01	0.96
1422511_a_at	Duplicate Gene Syn	OGFR	opioid growth factor receptor	Plasma Membrane	other	enkephalin, methionine	2.90E-06	2.31	5.47E-01	0.98	7.32E-01	1.01	1.70E-01	1.05	7.24E-01	0.99
1455975_x_at	Duplicate Gene Syn	RNF114	ring finger protein 114	Extracellular Space	other		6.14E-05	2.31	9.64E-01	1.00	8.23E-01	0.99	8.95E-01	0.99	8.13E-01	1.01
1454736_at		SOWAHC	sosondowah ankyrin repeat domain family member C	Nucleus	transcription regulator		5.03E-07	2.30	4.12E-01	0.96	3.02E-01	0.98	1.42E-04	1.27	2.04E-01	1.05
1454197_a_at	Duplicate Gene Syn	CCDC86	coiled-coil domain containing 86	Nucleus	other		2.80E-05	2.30	8.18E-02	0.90	3.12E-01	0.93	6.38E-02	1.10	9.34E-01	1.00
1423316_at		TMEM39A	transmembrane protein 39A	unknown	other		7.21E-06	2.29	4.84E-01	0.98	5.26E-01	0.97	6.39E-02	1.07	4.79E-01	1.03
1452291_at		ARAP2	ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 2	Cytoplasm	other		9.48E-04	2.28	8.39E-01	1.02	7.17E-01	1.04	1.42E-01	1.13	9.99E-03	1.30
1423804_a_at	Duplicate Gene Syn	IDI1	isopentenyl-diphosphate delta isomerase 1	Cytoplasm	enzyme		8.02E-05	2.28	9.52E-02	1.12	1.18E-02	1.30	1.62E-02	1.35	1.60E-02	1.50
1420522_at	Duplicate Gene Syn	Ccdc50	coiled-coil domain containing 50	Cytoplasm	other		2.37E-05	2.27	7.09E-01	0.98	2.27E-01	0.91	3.78E-02	1.12	3.38E-02	0.85
1422259_a_at	Duplicate Gene Syn	CCR5	chemokine (C-C motif) receptor 5 (gene/pseudogene)	Plasma Membrane	G-protein coupled receptor	maraviroc, vicriviroc, SCH 351125	5.17E-05	2.26	8.50E-01	0.99	3.58E-01	0.92	2.77E-01	0.96	5.65E-02	0.88
1431072_a_at	Duplicate Gene Syn	Ccdc50	coiled-coil domain containing 50	Cytoplasm	other		9.47E-06	2.25	6.85E-01	1.02	5.63E-01	0.98	2.63E-02	1.12	4.05E-01	0.96
1453721_a_at		SLC31A2	solute carrier family 31 (copper transporters), member 2	Plasma Membrane	transporter		4.46E-04	2.25	5.21E-01	1.04	4.38E-01	0.95	4.54E-01	1.05	6.16E-01	0.96
1417398_at	Duplicate Gene Syn	RRAS2	related RAS viral (r-ras) oncogene homolog 2	Plasma Membrane	enzyme		1.87E-04	2.25	3.96E-01	0.95	7.92E-01	0.97	7.69E-01	1.02	2.03E-01	0.91
1421366_at		CLEC5A	C-type lectin domain family 5, member A	Plasma Membrane	other		7.35E-05	2.25	8.17E-01	0.99	1.74E-01	0.89	8.16E-04	1.57	3.80E-01	0.94
1448689_at	Duplicate Gene Syn	RRAS2	related RAS viral (r-ras) oncogene homolog 2	Plasma Membrane	enzyme		4.21E-06	2.24	8.81E-01	1.00	8.58E-01	1.01	9.82E-01	1.00	7.82E-02	1.10

Probe Set Description							Stimulation Only		Compound Only				Stimulation and Compound			
							CpG vs. Medium		0.25 uM E6446 vs. Medium		1.25 uM E6446 vs. Medium		CpG + 0.25 uM E6446 vs. Medium		CpG + 1.25 uM E6446 vs. Medium	
1422473_at	Duplicate Gene Syn	PDE4B	phosphodiesterase 4B, cAMP-specific	Cytoplasm	enzyme	enprofylline, dyphylline, nitroglycerin, arofylline, tetomilast, L 869298, ibudilast, aminophylline, anagrelide, cilomilast, milrinone, rolipram, dipyridamole, L-826,141, ketotifen, roflumilast, tolbutamide, papaverine, theophylline, pentoxifylline, caffeine	1.46E-05	2.24	9.31E-01	1.01	6.32E-01	0.99	1.74E-03	1.49	1.62E-01	1.05
1427893_a_at		PMVK	phosphomevalonate kinase	Cytoplasm	kinase		2.16E-04	2.21	5.58E-01	1.03	9.22E-02	1.07	1.50E-04	1.25	7.25E-02	1.12
1419254_at		MTHFD2	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2, methenyltetrahydrofolate cyclohydrolase	Cytoplasm	enzyme		1.05E-05	2.21	7.64E-01	1.02	8.47E-02	0.93	1.58E-01	1.09	1.47E-01	0.91
1419477_at		CLEC2D	C-type lectin domain family 2, member D	Plasma Membrane	transmembrane receptor		5.31E-03	2.21	2.79E-01	0.85	6.14E-01	0.97	2.19E-03	1.42	4.97E-01	1.05
1422567_at		FAM129A	family with sequence similarity 129, member A	Cytoplasm	other		7.42E-06	2.20	7.19E-01	0.99	1.15E-01	0.90	7.88E-01	1.02	1.50E-01	0.94
1419879_s_at	Duplicate Gene Syn	TRIM25	tripartite motif containing 25	Cytoplasm	transcription regulator		1.38E-05	2.20	9.10E-01	1.00	7.54E-01	1.01	3.28E-01	1.03	2.11E-01	1.05
1417268_at		CD14	CD14 molecule	Plasma Membrane	transmembrane receptor		3.66E-06	2.18	7.08E-01	0.99	6.15E-01	0.99	3.93E-04	1.31	4.68E-01	1.03
1425025_at		TMEM106A	transmembrane protein 106A	unknown	other		1.54E-04	2.18	4.04E-01	1.07	4.63E-01	1.05	8.46E-01	1.01	8.25E-01	1.01
1449645_s_at		CCT3	chaperonin containing TCP1, subunit 3 (gamma)	Cytoplasm	other		4.12E-05	2.17	9.44E-01	1.00	6.49E-01	0.98	1.44E-01	1.08	7.44E-01	1.02
1460378_a_at	Duplicate Gene Syn	TES	testis derived transcript (3 LIM domains)	Plasma Membrane	other		4.14E-04	2.17	5.79E-01	0.96	5.92E-01	0.95	2.89E-01	1.09	6.37E-01	0.96
1422621_at	Duplicate Gene Syn	RANBP2	RAN binding protein 2	Nucleus	enzyme		8.37E-05	2.17	8.67E-01	1.01	7.99E-01	0.98	4.40E-01	1.07	1.37E-01	1.14
1427041_at		THEMIS2	thymocyte selection associated family member 2	unknown	other		7.90E-06	2.17	4.12E-01	0.97	3.48E-01	0.95	2.49E-02	1.12	5.53E-01	1.02
1423289_a_at		TMA16	translation machinery associated 16 homolog (S. cerevisiae)	unknown	other		1.89E-05	2.16	1.38E-01	1.06	3.52E-01	0.97	5.34E-02	1.13	9.28E-01	1.00
1448752_at		CA2	carbonic anhydrase II	Cytoplasm	enzyme	ethoxyzolamide, dichlorphenamide, methazolamide, diazoxide, hydrochlorothiazide, acetazolamide, trichloromethiazide, dorzolamide, chlorothiazide, dorzolamide/timolol, brinzolamide, quinethazone, chlorthalidone, benthiazide, sulfacetamide, topiramate	1.11E-05	2.16	9.55E-02	0.91	4.69E-02	0.95	3.88E-03	1.25	1.73E-01	0.98
1436337_at		TMEM243	transmembrane protein 243, mitochondrial	unknown	other		2.60E-03	2.15	3.21E-01	0.87	7.64E-01	1.05	5.04E-01	1.09	5.79E-01	0.94
1448748_at	Duplicate Gene Syn	PLEK	pleckstrin	Cytoplasm	other		1.60E-10	2.15	8.63E-01	1.00	3.61E-01	1.01	1.00E-05	1.21	2.20E-02	1.10
1450690_at	Duplicate Gene Syn	RANBP2	RAN binding protein 2	Nucleus	enzyme		6.95E-04	2.15	5.99E-01	1.04	6.18E-01	1.04	7.86E-02	1.21	7.17E-02	1.22
1416939_at		PPA1	pyrophosphatase (inorganic) 1	Cytoplasm	enzyme		1.64E-05	2.15	8.76E-01	1.01	6.81E-01	0.99	1.11E-01	1.06	1.10E-01	1.06
1424444_a_at		C19orf12	chromosome 19 open reading frame 12	unknown	other		7.13E-05	2.14	2.79E-01	0.96	9.11E-01	1.01	8.21E-01	1.01	3.82E-02	0.91
1424289_at		OSGIN2	oxidative stress induced growth inhibitor family member 2	unknown	other		2.28E-05	2.14	2.68E-01	0.96	8.48E-01	0.99	2.95E-02	1.14	3.77E-01	1.05
1431777_a_at		Hmgn3	high mobility group nucleosomal binding domain 3	Nucleus	other		3.95E-04	2.13	1.00E-01	0.94	2.47E-01	0.94	2.46E-02	1.13	6.12E-02	1.11
1438606_a_at	Duplicate Gene Syn	CLIC4	chloride intracellular channel 4	Plasma Membrane	ion channel		1.24E-05	2.13	3.71E-01	0.97	6.40E-01	0.99	1.97E-01	1.07	2.01E-02	1.08
1449875_s_at		H2-T9	histocompatibility 2, T region locus 9	unknown	other		3.58E-05	2.13	4.10E-01	0.97	6.12E-01	1.03	3.13E-01	0.96	8.30E-01	0.99
1450173_at		RIPK2	receptor-interacting serine-threonine kinase 2	Plasma Membrane	kinase		9.33E-05	2.12	9.72E-01	1.00	4.82E-01	1.04	3.55E-01	1.04	6.19E-01	0.98
1431646_a_at		STX6	syntaxin 6	Cytoplasm	transporter		2.44E-06	2.12	5.86E-01	1.02	6.10E-01	0.96	3.28E-02	1.08	5.59E-01	1.04
1433446_at		HMGCS1	3-hydroxy-3-methylglutaryl-CoA synthase 1 (soluble)	Cytoplasm	enzyme		5.97E-06	2.12	2.51E-03	1.17	2.60E-03	1.34	3.45E-04	1.51	1.21E-04	1.50
1416296_at		IL2RG	interleukin 2 receptor, gamma	Plasma Membrane	transmembrane receptor	aldesleukin, denileukin diftitox	3.14E-05	2.12	5.95E-01	1.02	9.39E-01	1.00	3.85E-03	1.26	4.23E-01	1.03
1419272_at		MYD88	myeloid differentiation primary response 88	Plasma Membrane	other		5.82E-05	2.11	8.66E-01	1.01	5.74E-01	1.03	8.86E-02	1.13	1.10E-01	1.11
1418929_at		IFT57	intraflagellar transport 57 homolog (CHlamydomonas)	Cytoplasm	other		5.84E-06	2.10	7.54E-01	0.99	4.03E-01	0.98	2.78E-03	1.22	5.30E-02	1.07
1422474_at	Duplicate Gene Syn	PDE4B	phosphodiesterase 4B, cAMP-specific	Cytoplasm	enzyme	enprofylline, dyphylline, nitroglycerin, arofylline, tetomilast, L 869298, ibudilast, aminophylline, anagrelide, cilomilast, milrinone, rolipram, dipyridamole, L-826,141, ketotifen, roflumilast, tolbutamide, papaverine, theophylline, pentoxifylline, caffeine	3.78E-05	2.10	7.32E-01	0.98	3.82E-01	1.03	1.00E-03	1.54	3.41E-01	1.08
1451458_at		TMEM2	transmembrane protein 2	unknown	other		1.49E-03	2.09	2.87E-01	0.90	4.55E-01	0.93	1.46E-01	0.85	6.03E-01	0.95
1423134_at		RILPL2	Rab interacting lysosomal protein-like 2	unknown	other		7.59E-05	2.09	2.86E-01	1.05	1.10E-01	1.08	4.06E-02	1.14	9.09E-02	1.09
1422260_x_at	Duplicate Gene Syn	CCR5	chemokine (C-C motif) receptor 5 (gene/pseudogene)	Plasma Membrane	G-protein coupled receptor	maraviroc, vicriviroc, SCH 351125	7.12E-05	2.09	8.94E-02	0.93	8.39E-01	1.01	6.78E-01	1.02	4.33E-01	0.96
1460257_a_at		MTHFS	5,10 methenyltetrahydrofolate synthetase (5-formyltetrahydrofolate cyclo-ligase)	Cytoplasm	enzyme		1.05E-04	2.07	2.82E-01	1.03	8.54E-01	1.00	4.67E-02	1.16	2.80E-02	1.08
1427334_s_at		KIAA1551	KIAA1551	unknown	other		3.12E-05	2.07	8.86E-01	0.99	9.91E-01	1.00	9.84E-03	1.18	8.66E-02	1.08
1448898_at		Ccl9	chemokine (C-C motif) ligand 9	Extracellular Space	cytokine		1.86E-03	2.07	8.14E-01	0.98	9.40E-01	0.99	1.20E-01	1.19	5.80E-01	1.04

							Stimulation Only		Compound Only				Stimulation and Compound			
			Probe Set Description				CpG vs. Medium		0.25 uM E6446 vs. Medium		1.25 uM E6446 vs. Medium		CpG + 0.25 uM E6446 vs. Medium		CpG + 1.25 uM E6446 vs. Medium	
1423103_at		RFX5	regulatory factor X, 5 (influences HLA class II expression)	Nucleus	transcription regulator		6.23E-06	2.06	2.35E-01	0.97	7.30E-01	0.98	3.43E-03	1.13	7.10E-01	1.01
1426324_at	Duplicate Gene Syn	HLA-B	major histocompatibility complex, class I, B	Plasma Membrane	transmembrane receptor		1.07E-05	2.06	4.76E-01	1.03	9.79E-01	1.00	3.18E-03	1.27	8.47E-02	1.07
1419132_at		TLR2	toll-like receptor 2	Plasma Membrane	transmembrane receptor		5.44E-05	2.06	1.98E-01	1.06	9.84E-01	1.00	8.68E-05	1.77	9.47E-02	1.07
1452225_at	Duplicate Gene Syn	SPPL2A	signal peptide peptidase like 2A	Plasma Membrane	peptidase		6.51E-06	2.05	8.45E-01	1.00	3.13E-01	1.03	2.31E-01	1.06	3.18E-02	1.11
1418244_at		NAA20	N(alpha)-acetyltransferase 20, NatB catalytic subunit	Cytoplasm	enzyme		4.23E-05	2.05	7.44E-01	0.99	4.62E-01	1.01	6.18E-01	0.98	1.04E-01	1.03
1419111_at		ING2	inhibitor of growth family, member 2	Nucleus	transcription regulator		8.91E-05	2.05	3.77E-01	1.02	4.71E-01	1.03	8.44E-01	0.99	3.08E-01	1.04
1434547_at		CPD	carboxypeptidase D	Extracellular Space	peptidase		1.07E-05	2.04	6.49E-01	0.98	7.60E-02	0.91	4.08E-01	0.96	8.34E-01	1.01
1424727_at	Duplicate Gene Syn	CCR5	chemokine (C-C motif) receptor 5 (gene/pseudogene)	Plasma Membrane	G-protein coupled receptor	maraviroc, vicriviroc, SCH 351125	8.35E-05	2.04	5.41E-01	0.98	4.62E-02	0.94	4.79E-01	0.98	4.30E-01	0.97
1450646_at		CYP51A1	cytochrome P450, family 51, subfamily A, polypeptide 1	Cytoplasm	enzyme	itraconazole	8.63E-05	2.04	3.71E-01	1.05	1.44E-02	1.23	1.47E-03	1.38	1.34E-03	1.40
1416401_at		CD82	CD82 molecule	Plasma Membrane	other		7.68E-06	2.03	5.76E-01	0.98	8.09E-01	0.99	5.18E-03	1.22	5.54E-01	0.99
1419537_at		TFEC	transcription factor EC	Nucleus	transcription regulator		1.07E-05	2.03	5.65E-01	0.97	4.09E-02	0.90	4.25E-04	1.33	1.10E-01	1.09
1418131_at		SAMHD1	SAM domain and HD domain 1	Nucleus	enzyme		2.50E-06	2.03	3.59E-01	0.98	4.10E-01	0.98	1.13E-02	0.93	5.00E-01	0.98
1416407_at		PEA15	phosphoprotein enriched in astrocytes 15	Cytoplasm	transporter		2.42E-05	2.02	6.65E-01	1.02	9.65E-01	1.00	5.95E-03	1.23	4.48E-02	1.13
1424246_a_at	Duplicate Gene Syn	TES	testis derived transcript (3 LIM domains)	Plasma Membrane	other		2.33E-05	2.02	9.32E-01	1.00	8.72E-01	1.00	6.14E-03	1.13	7.04E-01	1.01
1417333_at		RASA4	RAS p21 protein activator 4	Cytoplasm	other		1.88E-04	2.02	7.00E-01	1.02	3.70E-01	1.06	4.44E-02	1.19	1.43E-01	1.10
1435626_a_at		HERPUD1	homocysteine-inducible, endoplasmic reticulum stress-inducible, ubiquitin-like domain member 1	Cytoplasm	other		5.43E-06	2.02	7.89E-01	1.01	2.75E-01	0.95	1.82E-04	1.31	1.43E-01	1.03
1425412_at		NLRP3	NLR family, pyrin domain containing 3	Cytoplasm	other		2.59E-04	2.01	3.27E-01	1.06	4.52E-01	1.06	1.79E-02	1.22	2.12E-01	1.08
1437102_at		YTHDF1	YTH domain family, member 1	unknown	other		1.72E-05	2.01	2.79E-01	0.94	7.21E-01	0.99	3.46E-01	1.05	2.73E-01	0.97
1434372_at		AW112010	expressed sequence AW112010	unknown	other		1.90E-04	2.01	8.90E-02	0.96	9.44E-01	1.00	6.56E-02	1.11	7.13E-02	1.05
1452214_at		SKIL	SKI-like oncogene	Nucleus	transcription regulator		2.17E-05	2.01	7.35E-01	0.99	2.93E-01	0.96	3.45E-02	1.17	1.43E-01	1.04
1451780_at		BLNK	B-cell linker	Cytoplasm	other		1.40E-05	2.00	2.30E-01	0.96	6.46E-01	0.97	2.66E-01	1.04	3.07E-01	1.03
1434853_x_at		MKRN1	makorin ring finger protein 1	unknown	other		9.34E-05	0.50	4.80E-01	0.97	8.65E-01	1.01	9.19E-02	0.93	5.82E-01	1.03
1425503_at		GCNT2	glucosaminyl (N-acetyl) transferase 2, I-branching enzyme (I blood group)	Cytoplasm	enzyme		1.00E-03	0.50	8.72E-01	1.01	5.93E-01	0.96	8.50E-01	1.02	5.55E-01	1.05
1436097_x_at	Duplicate Gene Syn	ARHGAP9	Rho GTPase activating protein 9	Cytoplasm	other		4.76E-05	0.50	4.35E-01	0.97	8.39E-01	0.99	2.01E-01	0.93	2.27E-01	0.92
1449043_at		NAGA	N-acetylgalactosaminidase, alpha-	Cytoplasm	enzyme		1.20E-04	0.50	3.82E-01	0.97	1.52E-01	0.94	8.14E-02	0.92	1.44E-02	0.90
1416683_at		PLXNB2	plexin B2	Plasma Membrane	transmembrane receptor		2.86E-04	0.50	8.93E-01	0.99	8.16E-01	0.98	6.05E-01	0.97	9.26E-01	1.01
1421772_a_at	Duplicate Gene Syn	COX7A2L	cytochrome c oxidase subunit VIIa polypeptide 2 like	Cytoplasm	enzyme		1.13E-06	0.50	1.80E-01	1.02	3.33E-01	1.02	3.71E-01	0.96	8.51E-01	1.00
1453596_at		ID2	inhibitor of DNA binding 2, dominant negative helix-loop-helix protein	Nucleus	transcription regulator		4.41E-03	0.50	9.60E-01	0.99	7.68E-01	1.05	1.79E-01	1.17	6.02E-01	1.06
1416206_at		SIPA1	signal-induced proliferation-associated 1	Cytoplasm	other		2.05E-04	0.50	7.40E-01	1.01	7.60E-01	0.98	1.48E-01	0.93	9.57E-01	1.00
1417840_at		CEP19	centrosomal protein 19KDa	Cytoplasm	other		1.08E-04	0.50	2.17E-01	0.95	3.68E-01	0.96	1.22E-01	0.90	5.19E-01	0.97
1450015_x_at	Duplicate Gene Syn	SGPP1	sphingosine-1-phosphate phosphatase 1	Cytoplasm	phosphatase		5.04E-05	0.50	4.07E-01	0.94	1.47E-01	0.94	4.45E-02	0.90	9.53E-01	1.00
1449404_at		PIP4K2A	phosphatidylinositol-5-phosphate 4-kinase, type II, alpha	Cytoplasm	kinase		7.50E-05	0.50	7.29E-02	0.96	1.67E-01	0.93	1.62E-02	0.92	3.38E-01	0.97
1424059_at		SUV420H2	suppressor of variegation 4-20 homolog 2 (Drosophila)	Nucleus	enzyme		1.40E-04	0.50	9.57E-01	1.00	8.42E-01	1.01	2.96E-01	0.95	3.34E-01	1.04
1451421_a_at		ROGDI	rogdi homolog (Drosophila)	unknown	other		4.78E-05	0.49	1.26E-01	0.93	5.95E-01	0.98	7.79E-01	1.01	3.23E-01	0.94
1433756_at		S100PBP	S100P binding protein	Nucleus	other		5.26E-04	0.49	7.54E-01	0.97	9.85E-01	1.00	4.27E-01	1.06	5.46E-02	1.13
1451352_s_at	Duplicate Gene Syn	MTA3	metastasis associated 1 family, member 3	Nucleus	other		2.91E-05	0.49	9.70E-01	1.00	1.43E-01	0.95	2.53E-03	0.87	3.20E-02	0.92
1451353_at	Duplicate Gene Syn	TM6SF1	transmembrane 6 superfamily member 1	Plasma Membrane	other		5.76E-06	0.49	1.05E-01	0.96	9.83E-01	1.00	1.82E-02	0.94	2.90E-01	0.97
1427368_x_at		FES	feline sarcoma oncogene	Cytoplasm	kinase		1.14E-05	0.49	9.40E-01	1.00	6.05E-01	1.02	2.96E-01	0.97	1.82E-01	1.04
1417751_at		STK10	serine/threonine kinase 10	Cytoplasm	kinase		3.24E-05	0.49	4.17E-01	0.98	1.71E-01	0.97	2.79E-02	0.94	2.17E-02	0.92
1419538_at		FLT3	fms-related tyrosine kinase 3	Plasma Membrane	kinase	dovitinib, tandutinib, XL184, ponatinib, sorafenib, lestaurtinib, CGP 41251	3.28E-05	0.49	6.35E-01	0.99	7.12E-01	0.98	3.61E-01	0.97	4.01E-01	1.02
1427691_a_at		IFNAR2	interferon (alpha, beta and omega) receptor 2	Plasma Membrane	transmembrane receptor	interferon alfacon-1, PEG-interferon alfa-2a, interferon beta-1a, IFNA2, interferon alfa-2b/ribavirin, pegintron, interferon beta-1b	1.09E-05	0.49	4.09E-01	1.04	4.85E-01	1.02	1.88E-01	1.04	7.17E-02	1.06
1422476_at		IFI30	interferon, gamma-inducible protein 30	Cytoplasm	enzyme		6.61E-05	0.49	7.16E-01	0.99	8.22E-01	1.00	3.24E-01	1.02	3.06E-01	0.97
1422444_at		ITGA6	integrin, alpha 6	Plasma Membrane	transmembrane receptor		8.28E-04	0.49	6.14E-01	0.96	2.50E-01	0.90	1.11E-01	0.85	3.62E-01	0.93
1424829_at		TOR4A	torsin family 4, member A	unknown	other		6.26E-05	0.49	9.22E-02	0.93	9.27E-01	1.00	6.41E-01	0.98	9.21E-01	1.00
1427007_at		SASH3	SAM and SH3 domain containing 3	Cytoplasm	other		1.86E-05	0.49	5.62E-01	1.02	2.42E-01	1.06	9.53E-01	1.00	2.80E-01	1.04
1424169_at		TAX1BP3	Tax1 (human T-cell leukemia virus type I) binding protein 3	Cytoplasm	transcription regulator		1.72E-05	0.49	2.28E-01	1.04	1.37E-01	1.06	7.60E-01	0.99	2.12E-01	1.04
1449311_at		BACH1	BTB and CNC homology 1, basic leucine zipper transcription factor 1	Nucleus	transcription regulator		9.46E-04	0.49	9.92E-01	1.00	2.03E-01	0.88	7.26E-02	0.79	3.32E-02	0.76
1432263_a_at	Duplicate Gene Syn	COX7A2L	cytochrome c oxidase subunit VIIa polypeptide 2 like	Cytoplasm	enzyme		2.83E-05	0.49	5.68E-01	1.02	3.69E-01	1.02	2.77E-01	0.95	4.41E-01	0.98
1426812_a_at		FAM129B	family with sequence similarity 129, member B	Cytoplasm	other		1.96E-05	0.49	8.12E-01	1.01	6.93E-01	0.98	1.64E-01	0.94	6.57E-01	0.98
1422123_s_at	Duplicate Gene Syn	Ceacam1/Ceacam2	carcinoembryonic antigen-related cell adhesion molecule 1	Plasma Membrane	other		1.53E-03	0.49	5.81E-02	1.05	5.30E-01	0.98	4.68E-02	0.93	4.45E-03	0.91
1416188_at		GM2A	GM2 ganglioside activator	Cytoplasm	enzyme		1.48E-02	0.49	7.13E-01	0.93	8.12E-01	0.95	8.49E-01	0.97	4.56E-01	0.87
1423593_a_at	Duplicate Gene Syn	CSF1R	colony stimulating factor 1 receptor	Plasma Membrane	kinase	sunitinib, pazopanib	8.32E-05	0.49	9.28E-01	1.01	5.96E-01	1.04	9.29E-01	1.00	9.50E-01	1.00
1455990_at	Duplicate Gene Syn	KIF23	kinesin family member 23	Cytoplasm	other		3.74E-05	0.49	4.10E-01	0.98	7.96E-01	1.01	6.58E-01	0.99	2.36E-01	1.04
1421317_x_at	Duplicate Gene Syn	MYB	v-myb myeloblastosis viral oncogene homolog (avian)	Nucleus	transcription regulator		1.38E-05	0.48	9.35E-01	1.00	6.48E-01	0.98	6.68E-02	0.96	2.47E-01	1.02
1434866_x_at		CPT1A	carnitine palmitoyltransferase 1A (liver)	Cytoplasm	enzyme	perhexiline	3.98E-05	0.48	1.87E-01	0.95	8.17E-02	0.94	1.49E-01	0.83	4.87E-01	0.97
1426245_s_at	Duplicate Gene Syn	MAPRE2	microtubule-associated protein, RP/EB family, member 2	Cytoplasm	other		1.05E-03	0.48	3.21E-01	0.95	4.27E-01	0.96	1.64E-01	0.91	6.52E-01	0.98
1426169_a_at		LAT2	linker for activation of T cells family, member 2	Plasma Membrane	other		1.33E-02	0.48	6.56E-01	0.93	9.34E-01	1.02	5.55E-01	1.10	6.01E-01	0.91
1434045_at		CDKN1B	cyclin-dependent kinase inhibitor 1B (p27, Kip1)	Nucleus	kinase		8.10E-05	0.48	6.16E-01	1.04	9.98E-01	1.00	3.44E-01	0.92	4.36E-01	1.08
1432264_x_at	Duplicate Gene Syn	COX7A2L	cytochrome c oxidase subunit VIIa polypeptide 2 like	Cytoplasm	enzyme		2.61E-05	0.48	8.33E-01	0.99	8.77E-01	1.00	1.56E-01	0.94	2.63E-01	0.96
1423394_at		PCYOX1	prenylcysteine oxidase 1	Cytoplasm	enzyme		1.17E-05	0.48	1.01E-01	0.97	4.62E-01	1.02	4.31E-03	0.90	8.65E-01	0.99

							Stimulation Only		Compound Only				Stimulation and Compound			
			Probe Set Description				CpG vs. Medium		0.25 uM E6446 vs. Medium		1.25 uM E6446 vs. Medium		CpG + 0.25 uM E6446 vs. Medium		CpG + 1.25 uM E6446 vs. Medium	
1416647_at		BCKDHA	branched chain keto acid dehydrogenase E1, alpha polypeptide	Cytoplasm	enzyme		6.03E-05	0.48	5.84E-01	0.97	9.00E-01	1.01	2.34E-01	0.95	9.65E-01	1.00
1416914_s_at							8.18E-06	0.48	5.88E-01	0.99	6.93E-01	1.01	7.98E-01	0.99	1.64E-01	1.04
1421188_at		CCR2	chemokine (C-C motif) receptor 2	Plasma Membrane	G-protein coupled receptor		2.53E-05	0.48	1.99E-01	1.03	1.10E-01	0.97	4.50E-02	0.90	1.38E-01	1.06
1415823_at	Duplicate Gene Syn	Scd2	stearoyl-Coenzyme A desaturase 2	Cytoplasm	enzyme		1.39E-04	0.48	1.79E-01	1.11	2.43E-02	1.17	1.64E-02	1.15	1.69E-03	1.30
1423182_at		TNFRSF13B	tumor necrosis factor receptor superfamily, member 13B	Plasma Membrane	transmembrane receptor		5.90E-06	0.48	1.42E-01	0.96	2.42E-01	0.96	3.75E-02	0.91	6.85E-02	0.93
1415995_at		CASP6	caspase 6, apoptosis-related cysteine peptidase	Cytoplasm	peptidase		7.77E-05	0.48	5.20E-01	0.99	4.67E-01	0.98	2.88E-02	0.90	3.72E-01	0.97
1417534_at	Duplicate Gene Syn	ITGB5	integrin, beta 5	Plasma Membrane	other	EMD121974	3.49E-06	0.48	9.00E-01	1.00	3.11E-01	1.06	1.59E-02	0.90	7.10E-01	1.00
1453748_a_at	Duplicate Gene Syn	KIF23	kinesin family member 23	Cytoplasm	other		1.30E-03	0.48	9.03E-01	0.99	8.56E-01	0.98	7.70E-01	0.98	1.89E-01	1.15
1417038_at		Sept9	septin 9	Cytoplasm	enzyme		9.00E-04	0.48	6.61E-01	0.96	8.88E-01	0.98	6.06E-01	0.96	2.32E-01	0.91
1426236_a_at		GLUL	glutamate-ammonia ligase	Cytoplasm	enzyme		5.63E-05	0.48	3.99E-01	0.94	3.51E-01	0.89	3.88E-01	0.95	1.49E-02	0.87
1434856_at		ANKRD44	ankyrin repeat domain 44	unknown	other		1.37E-05	0.48	1.67E-01	1.04	4.30E-01	1.04	6.07E-02	0.90	2.08E-01	1.06
1428018_a_at		CD300C	CD300c molecule	Plasma Membrane	transmembrane receptor		5.90E-04	0.47	2.73E-01	1.03	4.19E-02	1.05	6.60E-01	0.98	1.38E-01	1.06
1428122_s_at		MVB12B	multivesicular body subunit 12B	Cytoplasm	other		7.05E-05	0.47	3.34E-01	0.96	5.79E-01	0.96	3.98E-02	0.87	3.12E-01	0.96
1428242_at		HMHA1	histocompatibility (minor) HA-1	Cytoplasm	transporter		2.25E-05	0.47	2.52E-01	1.02	6.36E-01	1.03	1.82E-01	0.97	5.40E-02	1.09
1420905_at		IL17RA	interleukin 17 receptor A	Plasma Membrane	transmembrane receptor		7.03E-05	0.47	6.44E-01	1.03	8.97E-01	1.01	4.23E-01	0.94	4.38E-01	1.04
1450494_x_at	Duplicate Gene Syn	Ceacam1/Ceacam2	carcinoembryonic antigen related cell adhesion molecule 1	Plasma Membrane	other		6.13E-04	0.47	8.30E-01	0.98	3.87E-01	0.94	3.03E-02	0.83	1.04E-01	0.86
1433725_at		ACVR1B	activin A receptor, type IB	Plasma Membrane	kinase		3.19E-04	0.47	1.04E-01	0.90	7.53E-01	0.99	1.72E-01	0.92	1.01E-01	0.95
1425263_a_at		MBP	myelin basic protein	Extracellular Space	other		4.33E-04	0.47	6.24E-01	0.95	4.58E-02	0.84	3.04E-02	0.83	7.19E-02	0.84
1436954_at		WIPF1	WAS/WASL interacting protein family, member 1	Cytoplasm	other		4.29E-06	0.47	3.11E-01	0.96	2.39E-01	0.94	3.95E-03	0.79	1.97E-01	0.92
1417135_at	Duplicate Gene Syn	SRPK2	SRSF protein kinase 2	Nucleus	kinase		1.07E-04	0.47	8.52E-01	0.99	1.11E-01	0.92	3.69E-03	0.78	2.49E-02	0.86
1434017_at	Duplicate Gene Syn	ZNRF2	zinc and ring finger 2	unknown	other		1.51E-06	0.47	4.10E-01	0.97	5.16E-01	0.99	8.08E-02	0.93	6.43E-01	1.01
1416529_at		EMP1	epithelial membrane protein 1	Plasma Membrane	other		3.02E-05	0.47	1.64E-01	0.97	6.59E-01	0.99	1.64E-02	0.80	9.74E-01	1.00
1448406_at		EID1	EP300 interacting inhibitor of differentiation 1	Nucleus	transcription regulator		3.54E-05	0.47	7.98E-01	0.98	2.29E-02	0.88	2.10E-02	0.76	3.09E-02	0.79
1415897_a_at		MGST1	microsomal glutathione S-transferase 1	Cytoplasm	enzyme		2.20E-05	0.47	9.18E-01	1.00	5.76E-01	0.98	1.46E-01	0.94	2.10E-01	1.06
1452067_at		NAAA	N-acylethanolamine acid amidase	Cytoplasm	enzyme		3.68E-04	0.47	8.86E-01	0.99	1.59E-01	0.93	3.81E-03	0.87	5.97E-02	0.91
1448878_at		MXD3	MAX dimerization protein 3	Nucleus	transcription regulator		2.87E-04	0.46	2.76E-01	0.96	7.13E-01	0.99	1.27E-02	0.86	1.84E-01	0.95
1440964_s_at	Duplicate Gene Syn	CBFA2T3	core-binding factor, runt domain, alpha subunit 2; translocated to, 3	Nucleus	transcription regulator		1.77E-04	0.46	6.72E-01	0.98	4.33E-01	0.97	1.21E-01	0.92	3.66E-02	0.91
1420822_s_at	Duplicate Gene Syn	SGPP1	sphingosine-1-phosphate phosphatase 1	Cytoplasm	phosphatase		5.46E-04	0.46	8.92E-01	1.01	9.25E-01	1.01	2.99E-01	0.87	8.13E-01	1.03
1449127_at		SELPLG	selectin P ligand	Plasma Membrane	other		2.54E-06	0.46	9.79E-01	1.00	7.73E-01	1.01	2.77E-02	0.93	1.66E-01	0.96
1455291_s_at	Duplicate Gene Syn	ZNRF2	zinc and ring finger 2	unknown	other		1.05E-04	0.46	5.66E-01	0.97	8.93E-01	0.99	1.50E-01	0.86	2.64E-01	1.07
1434831_a_at	Duplicate Gene Syn	FOXO3	forkhead box O3	Nucleus	transcription regulator		7.08E-05	0.46	6.71E-01	0.98	9.76E-01	1.00	4.88E-01	0.97	3.57E-01	1.04
1451024_at		S1PR4	sphingosine-1-phosphate receptor 4	Plasma Membrane	G-protein coupled receptor	fingolimod	4.35E-04	0.46	6.86E-01	0.99	1.47E-01	1.04	1.43E-02	0.86	1.29E-01	0.97
1417640_at		CD79B	CD79b molecule, immunoglobulin-associated beta	Plasma Membrane	transmembrane receptor		1.19E-04	0.46	3.33E-01	0.95	6.41E-01	0.98	1.80E-01	0.92	2.30E-01	0.93
1435945_a_at		KCNN4	potassium intermediate/small conductance calcium-activated channel, subfamily N, member 4	Plasma Membrane	ion channel	clotrimazole, ICA 17043	4.75E-05	0.46	8.25E-01	0.99	9.30E-01	1.00	1.62E-01	0.93	9.04E-02	0.92
1418643_at		TSPAN13	tetraspanin 13	Plasma Membrane	other		1.16E-06	0.46	4.12E-01	0.98	3.72E-01	0.97	9.23E-03	0.87	1.44E-02	0.92
1418192_at		MNT	MNT, MAX dimerization protein	Nucleus	transcription regulator		2.84E-05	0.46	2.28E-01	0.96	8.62E-01	1.01	4.37E-01	0.96	8.38E-01	1.01
1424850_at		MAP3K1	mitogen-activated protein kinase kinase kinase 1, E3 ubiquitin protein ligase	Cytoplasm	kinase		6.11E-05	0.46	8.35E-01	0.99	6.26E-01	1.03	5.70E-02	0.92	5.43E-01	1.02
1434832_at	Duplicate Gene Syn	FOXO3	forkhead box O3	Nucleus	transcription regulator		2.24E-03	0.46	6.16E-01	0.96	4.18E-01	1.05	3.57E-01	0.95	7.49E-01	1.03
1436182_at	Duplicate Gene Syn	SATB1	SATB homeobox 1	Nucleus	transcription regulator		4.30E-04	0.46	2.35E-01	0.92	9.83E-01	1.00	2.80E-01	0.94	3.37E-01	1.04
1434487_at		MEF2D	myocyte enhancer factor 2D	Nucleus	transcription regulator		7.61E-05	0.46	3.16E-02	0.93	4.00E-01	0.98	3.08E-01	0.97	2.80E-02	1.09
1448167_at		IFNGR1	interferon gamma receptor 1	Plasma Membrane	transmembrane receptor	interferon gamma-1b	3.87E-03	0.46	7.94E-01	0.96	9.84E-01	1.00	7.35E-01	0.95	4.82E-01	0.90
1430391_a_at	Duplicate Gene Syn	ST8SIA4	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 4	Cytoplasm	enzyme		2.27E-05	0.45	3.76E-01	0.96	4.65E-02	0.90	3.77E-02	0.89	4.32E-03	0.89
1424249_a_at	Duplicate Gene Syn	ARHGAP9	Rho GTPase activating protein 9	Cytoplasm	other		6.42E-05	0.45	1.63E-01	0.92	4.97E-01	0.96	6.32E-02	0.87	1.54E-01	0.90
1433711_s_at	Duplicate Gene Syn	SESN1	sestrin 1	Nucleus	other		4.86E-05	0.45	8.43E-01	1.00	6.16E-01	1.01	2.53E-01	1.04	9.25E-01	1.00
1450626_at		MANBA	mannosidase, beta A, lysosomal	Cytoplasm	enzyme		4.19E-05	0.45	8.60E-01	1.01	4.17E-01	1.04	1.35E-01	0.91	2.29E-01	1.06
1419872_at	Duplicate Gene Syn	CSF1R	colony stimulating factor 1 receptor	Plasma Membrane	kinase	sunitinib, pazopanib	1.09E-04	0.45	4.89E-01	0.98	1.27E-01	0.96	6.86E-02	0.92	1.30E-01	0.96
1421618_at		MYO1F	myosin IF	Cytoplasm	other		3.08E-05	0.45	7.72E-01	0.99	8.67E-01	0.99	5.49E-01	0.97	7.69E-01	1.01
1424032_at		HVCN1	hydrogen voltage-gated channel 1	unknown	ion channel		3.24E-04	0.45	6.11E-01	1.03	1.79E-01	1.09	4.22E-01	0.94	4.77E-02	1.14
1418840_at		PDCD4	programmed cell death 4 (neoplastic transformation inhibitor)	Nucleus	other		3.03E-05	0.45	4.68E-01	0.94	7.27E-01	0.97	2.39E-01	0.91	7.45E-01	0.99
1420928_at		ST6GAL1	ST6 beta-galactosamide alpha-2,6-sialyltranferase 1	Cytoplasm	enzyme		9.02E-05	0.45	9.43E-01	1.00	6.38E-02	1.04	2.41E-01	0.97	1.92E-01	0.96
1427074_at	Duplicate Gene Syn	PCMTD2	protein-L-isoaspartate (D-aspartate) O-methyltransferase domain containing 2	Cytoplasm	enzyme		1.82E-04	0.45	7.50E-01	0.99	4.30E-01	0.98	1.59E-01	0.93	3.36E-01	1.04
1419156_at		SOX4	SRY (sex determining region Y)-box 4	Nucleus	transcription regulator		2.44E-05	0.45	7.69E-01	0.98	4.85E-01	0.98	2.36E-01	1.05	9.24E-01	1.00
1451196_at		YPEL5	yippee-like 5 (Drosophila)	unknown	other		2.07E-04	0.45	7.11E-01	0.99	4.15E-01	0.95	1.21E-01	0.91	3.73E-01	0.95
1417136_s_at	Duplicate Gene Syn	SRPK2	SRSF protein kinase 2	Nucleus	kinase		8.79E-06	0.45	5.77E-01	1.02	3.70E-01	0.94	3.31E-02	0.83	2.03E-02	0.87
1439389_s_at	Duplicate Gene Syn	MYADM	myeloid-associated differentiation marker	Nucleus	other		1.54E-04	0.45	4.86E-01	1.03	6.25E-02	0.94	9.88E-02	0.87	2.65E-01	0.94
1438321_x_at		FAM63A	family with sequence similarity 63, member A	unknown	other		1.24E-04	0.45	6.31E-01	0.97	3.25E-01	0.93	3.79E-02	0.87	3.84E-01	0.96
1449619_s_at	Duplicate Gene Syn	ARHGAP9	Rho GTPase activating protein 9	Cytoplasm	other		1.92E-04	0.45	1.91E-01	0.91	2.05E-01	0.92	1.39E-01	0.89	1.15E-01	0.87
1420821_at	Duplicate Gene Syn	SGPP1	sphingosine-1-phosphate phosphatase 1	Cytoplasm	phosphatase		1.89E-03	0.45	8.96E-01	1.02	6.34E-01	0.94	3.39E-01	0.82	5.79E-01	1.09
1460555_at		FAM65B	family with sequence similarity 65, member B	unknown	other		1.62E-04	0.44	7.25E-01	1.02	6.15E-01	1.03	2.72E-01	0.94	1.35E-01	1.08
1423100_at		FOS	FBJ murine osteosarcoma viral oncogene homolog	Nucleus	transcription regulator		1.61E-05	0.44	5.10E-03	0.85	4.63E-01	0.95	4.64E-02	1.09	2.30E-02	0.87
1422734_a_at	Duplicate Gene Syn	MYB	v-myb myeloblastosis viral oncogene homolog (avian)	Nucleus	transcription regulator		3.19E-04	0.44	7.88E-01	0.96	8.45E-01	0.98	7.00E-01	0.96	7.57E-01	1.02
1428083_at		Neat1	nuclear paraspeckle assembly transcript 1 (non-protein coding)	Nucleus	other		7.74E-04	0.44	3.67E-01	1.08	3.34E-01	1.09	8.69E-01	1.01	2.84E-02	1.27
1456133_x_at	Duplicate Gene Syn	ITGB5	integrin, beta 5	Plasma Membrane	other	EMD121974	3.96E-04	0.44	6.79E-02	1.04	8.29E-01	0.99	8.44E-03	0.83	2.67E-02	0.93
1440865_at		Ifitm6	interferon induced transmembrane protein 6	unknown	other		8.62E-06	0.44	8.30E-01	1.01	3.37E-01	1.04	8.25E-02	0.93	7.76E-01	1.02
1418582_at	Duplicate Gene Syn	CBFA2T3	core-binding factor, runt domain, alpha subunit 2; translocated to, 3	Nucleus	transcription regulator		1.84E-04	0.44	3.71E-01	1.04	6.48E-01	1.02	4.27E-01	0.97	1.82E-01	0.94
1418649_at		EGLN3	egl nine homolog 3 (C. elegans)	Cytoplasm	enzyme		1.71E-04	0.44	7.57E-01	0.99	6.56E-01	1.01	8.00E-01	1.01	8.54E-03	1.06
1423321_at	Duplicate Gene Syn	MYADM	myeloid-associated differentiation marker	Nucleus	other		2.62E-05	0.44	2.90E-01	0.96	7.12E-02	0.95	2.27E-02	0.92	3.41E-03	0.92
1419873_s_at	Duplicate Gene Syn	CSF1R	colony stimulating factor 1 receptor	Plasma Membrane	kinase	sunitinib, pazopanib	3.57E-05	0.44	7.68E-01	1.01	6.75E-01	0.98	3.07E-01	0.96	4.78E-01	0.97
1456393_at		BBIP1	BBSome interacting protein 1	Cytoplasm	other		2.21E-04	0.44	4.55E-01	1.05	7.01E-01	1.03	4.55E-01	0.95	5.32E-02	1.20
1452001_at		NFE2	nuclear factor (erythroid-derived 2), 45kDa	Nucleus	transcription regulator		2.16E-04	0.44	6.14E-01	0.96	4.69E-01	0.96	3.59E-01	0.94	1.99E-01	0.92
1422631_at		AHR	aryl hydrocarbon receptor	Nucleus	ligand-dependent nuclear receptor		7.93E-04	0.44	5.77E-01	1.03	3.99E-01	0.96	9.59E-02	0.84	3.22E-01	0.96
1434930_at		TPCN1	two pore segment channel 1	Plasma Membrane	ion channel		2.05E-04	0.44	8.58E-01	1.01	8.08E-01	1.02	1.97E-01	0.90	7.05E-01	0.98

			Probe Set Description				Stimulation Only		Compound Only				Stimulation and Compound			
							CpG vs. Medium		0.25 uM E6446 vs. Medium		1.25 uM E6446 vs. Medium		CpG + 0.25 uM E6446 vs. Medium		CpG + 1.25 uM E6446 vs. Medium	
1452141_a_at		SEPP1	selenoprotein P, plasma, 1	Extracellular Space	other		1.79E-05	0.43	5.07E-01	1.02	2.21E-01	1.05	7.68E-02	0.91	3.92E-01	1.03
1418396_at		GPSM3	G-protein signaling modulator 3	Cytoplasm	other		2.50E-05	0.43	8.96E-01	1.00	2.05E-01	0.97	1.36E-01	0.96	5.44E-02	0.94
1434010_at		FAM117B	family with sequence similarity 117, member B	unknown	other		3.47E-05	0.43	4.70E-01	0.97	6.23E-01	0.97	1.73E-01	0.92	9.60E-01	1.00
1415834_at		DUSP6	dual specificity phosphatase 6	Cytoplasm	phosphatase		1.77E-03	0.43	2.76E-01	0.86	7.12E-01	0.95	3.36E-01	0.89	3.18E-01	0.88
1450194_a_at	Duplicate Gene Syn	MYB	v-myb myeloblastosis viral oncogene homolog (avian)	Nucleus	transcription regulator		1.99E-03	0.43	6.97E-01	0.97	3.49E-01	0.93	9.71E-01	1.00	8.57E-01	1.01
1421402_at	Duplicate Gene Syn	MTA3	metastasis associated 1 family, member 3	Nucleus	other		7.62E-05	0.43	1.41E-01	0.97	1.66E-01	0.93	4.63E-03	0.86	6.44E-03	0.93
1423414_at	Duplicate Gene Syn	PTGS1	prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase)	Cytoplasm	enzyme	acetaminophen/pentazocine, acetaminophen/clemastine/pseudoephedrine, aspirin/butalbital/caffeine, acetaminophen/caffeine/dihydrocodeine, aspirin/hydrocodone, aspirin/oxycodone, acetaminophen/aspirin/caffeine, aspirin/pravastatin, acetaminophen/dexbrompheniramine/pseudoephedrine, aspirin/meprobamate, aspirin/caffeine/propoxyphen	6.97E-04	0.43	2.16E-01	0.93	1.42E-01	0.92	3.41E-02	0.87	3.47E-02	0.84
1426708_at		ANTXR2	anthrax toxin receptor 2	Plasma Membrane	transmembrane receptor		1.06E-05	0.43	7.68E-01	1.01	9.00E-01	1.01	1.23E-01	0.89	3.62E-01	1.05
1420979_at	Duplicate Gene Syn	PAK1	p21 protein (Cdc42/Rac)-activated kinase 1	Cytoplasm	kinase		2.80E-06	0.43	2.07E-01	0.97	1.41E-02	0.92	1.46E-01	0.96	5.24E-01	0.99
1435666_at		MAST3	microtubule associated serine/threonine kinase 3	unknown	kinase		2.99E-05	0.43	4.76E-01	0.96	2.86E-01	1.04	5.77E-01	0.98	2.74E-01	1.05
1418944_at		CYSLTR1	cysteinyl leukotriene receptor 1	Plasma Membrane	G-protein coupled receptor	zeneca ZD 3523, montelukast, zafirlukast, pranlukast	4.80E-05	0.43	5.09E-01	0.95	4.36E-01	0.93	1.91E-02	0.75	3.82E-03	0.78
1431804_a_at		SP3	Sp3 transcription factor	Nucleus	transcription regulator		1.82E-02	0.43	5.01E-01	0.81	7.75E-01	0.91	5.73E-01	0.88	2.10E-01	0.77
1424443_at	Duplicate Gene Syn	TM6SF1	transmembrane 6 superfamily member 1	Plasma Membrane	other		6.82E-05	0.43	9.58E-01	1.00	5.34E-01	0.97	1.83E-01	0.88	3.74E-01	1.06
1448547_at	Duplicate Gene Syn	RASSF3	Ras association (RalGDS/AF-6) domain family member 3	unknown	other		2.29E-04	0.42	5.03E-01	0.96	2.16E-01	0.94	4.26E-03	0.75	1.23E-03	0.81
1424704_at		RUNX2	runt-related transcription factor 2	Nucleus	transcription regulator		3.25E-04	0.42	3.80E-01	0.94	9.16E-01	0.99	7.03E-01	0.97	4.76E-01	1.07
1436448_a_at	Duplicate Gene Syn	PTGS1	prostaglandin-endoperoxide synthase 1 (prostaglandin G/H synthase and cyclooxygenase)	Cytoplasm	enzyme	acetaminophen/pentazocine, acetaminophen/clemastine/pseudoephedrine, aspirin/butalbital/caffeine, acetaminophen/caffeine/dihydrocodeine, aspirin/hydrocodone, aspirin/oxycodone, acetaminophen/aspirin/caffeine, aspirin/pravastatin, acetaminophen/dexbrompheniramine/pseudoephedrine, aspirin/meprobamate, aspirin/caffeine/propoxyphen	3.93E-05	0.42	9.21E-01	1.01	1.51E-01	1.09	2.07E-01	0.88	9.28E-01	1.01
1452217_at		AHNAK	AHNAK nucleoprotein	Nucleus	other		1.87E-03	0.42	8.36E-01	1.03	7.63E-01	0.96	9.20E-01	0.99	6.11E-01	1.07
1417513_at		EVI5	ecotropic viral integration site 5	unknown	other		2.16E-05	0.42	4.56E-01	1.03	2.65E-01	0.96	5.00E-02	0.89	1.95E-01	0.95
1422824_s_at		EPS8	epidermal growth factor receptor pathway substrate 8	Plasma Membrane	peptidase		3.64E-04	0.42	8.64E-01	0.99	8.42E-01	0.99	1.97E-02	0.76	9.72E-01	1.00
1423632_at		GPR146	G protein-coupled receptor 146	Plasma Membrane	G-protein coupled receptor		1.07E-03	0.42	7.76E-01	0.99	9.07E-02	1.08	1.29E-02	0.86	3.79E-01	0.97
1420970_at	Duplicate Gene Syn	ADCY7	adenylate cyclase 7	Plasma Membrane	enzyme		4.08E-07	0.42	4.03E-01	1.04	8.54E-01	0.99	7.47E-01	1.02	2.84E-03	1.13
1448318_at		PLIN2	perilipin 2	Plasma Membrane	other		4.17E-05	0.42	6.86E-01	1.03	2.45E-01	1.05	1.67E-02	0.84	9.90E-01	1.00
1438931_s_at	Duplicate Gene Syn	SESN1	sestrin 1	Nucleus	other		6.19E-05	0.41	8.08E-01	0.99	1.72E-01	0.93	5.53E-01	0.94	4.82E-01	1.06
1429775_a_at							4.99E-04	0.41	5.35E-01	1.04	3.28E-01	1.04	1.15E-01	0.89	2.86E-01	1.06
1416882_at		RGS10	regulator of G-protein signaling 10	Cytoplasm	other		2.57E-05	0.41	5.02E-01	0.98	1.17E-01	1.05	5.56E-02	0.94	6.34E-01	0.99
1448477_at		CHST12	carbohydrate (chondroitin 4) sulfotransferase 12	Cytoplasm	enzyme		1.47E-05	0.41	5.13E-01	0.98	8.69E-01	1.01	1.15E-02	0.89	7.97E-01	0.99
1450718_at		SH2B2	SH2B adaptor protein 2	Cytoplasm	other		9.28E-06	0.41	5.57E-01	1.03	8.16E-01	1.01	7.94E-01	1.01	2.76E-01	1.07
1415822_at	Duplicate Gene Syn	Scd2	stearoyl-Coenzyme A desaturase 2	Cytoplasm	enzyme		1.37E-05	0.41	3.21E-02	1.12	3.76E-03	1.25	2.17E-02	1.15	2.40E-03	1.37
1418294_at		EPB41L4B	erythrocyte membrane protein band 4.1 like 4B	unknown	transporter		8.41E-05	0.41	3.51E-01	0.94	2.54E-01	0.93	7.32E-01	0.98	5.93E-01	0.98
1460245_at		KLRD1	killer cell lectin-like receptor subfamily D, member 1	Plasma Membrane	transmembrane receptor		6.95E-05	0.41	9.05E-01	1.00	6.99E-01	0.99	4.82E-01	1.06	3.49E-03	1.10
1436050_x_at		HES6	hairy and enhancer of split 6 (Drosophila)	Nucleus	transcription regulator		1.93E-05	0.41	9.95E-03	0.93	1.32E-01	0.98	4.80E-01	0.97	8.04E-01	0.99
1451361_a_at		PNPLA7	patatin-like phospholipase domain containing 7	unknown	enzyme		7.21E-05	0.41	3.14E-01	1.08	2.24E-01	1.11	8.43E-01	0.99	2.52E-02	1.18
1422751_at		TLE1	transducin-like enhancer of split 1 (E(sp1) homolog, Drosophila)	Nucleus	transcription regulator		5.09E-05	0.41	9.34E-01	0.99	3.51E-01	0.89	4.90E-02	0.79	1.46E-02	0.76
1417266_at	Duplicate Gene Syn	Ccl6	chemokine (C-C motif) ligand 6	Extracellular Space	cytokine		4.33E-04	0.41	2.08E-01	0.94	2.01E-01	0.92	3.22E-02	0.86	3.30E-02	0.86
1432543_a_at		KLF13	Kruppel-like factor 13	Nucleus	transcription regulator		7.14E-05	0.41	1.79E-01	0.87	2.22E-01	0.93	1.42E-02	0.80	2.06E-02	0.87
1420756_at		FUT7	fucosyltransferase 7 (alpha (1,3) fucosyltransferase)	Cytoplasm	enzyme		4.48E-04	0.40	4.10E-01	0.96	8.94E-01	1.01	1.28E-01	0.92	1.23E-01	0.92
1429173_at		DNASE1L1	deoxyribonuclease I-like 1	Cytoplasm	enzyme		5.66E-05	0.40	7.64E-01	0.99	4.17E-01	1.02	1.03E-02	0.90	7.39E-01	1.02
1455871_s_at		RPL13	ribosomal protein L13	Cytoplasm	other		2.24E-05	0.40	2.91E-01	1.05	9.83E-01	1.00	7.04E-01	0.99	8.23E-01	0.99
1451731_at		ABCA3	ATP-binding cassette, sub-family A (ABC1), member 3	Plasma Membrane	transporter		2.46E-04	0.40	5.49E-01	0.96	3.36E-01	0.94	2.47E-01	0.92	9.14E-01	0.99
1452389_at		CD27	CD27 molecule	Plasma Membrane	transmembrane receptor		1.47E-04	0.40	2.38E-01	0.93	6.98E-02	0.89	6.98E-01	0.98	1.26E-01	0.94
1422532_at		XPC	xeroderma pigmentosum, complementation group C	Nucleus	other		3.40E-04	0.40	7.60E-01	0.98	5.40E-01	0.96	2.23E-01	0.91	5.20E-01	0.96
1419810_x_at	Duplicate Gene Syn	ARHGAP9	Rho GTPase activating protein 9	Cytoplasm	other		1.08E-04	0.40	8.64E-03	0.89	1.36E-01	0.97	6.42E-02	0.89	4.35E-02	0.94
1416008_at	Duplicate Gene Syn	SATB1	SATB homeobox 1	Nucleus	transcription regulator		8.66E-06	0.40	5.70E-01	0.96	9.73E-01	1.00	8.41E-02	0.90	8.35E-01	0.99
1454699_at	Duplicate Gene Syn	SESN1	sestrin 1	Nucleus	other		4.54E-05	0.40	8.66E-01	0.99	6.15E-01	0.97	9.33E-01	1.01	4.62E-01	1.05
1419186_a_at	Duplicate Gene Syn	ST8SIA4	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 4	Cytoplasm	enzyme		7.43E-06	0.40	1.93E-01	0.95	2.16E-01	0.95	4.07E-02	0.85	1.34E-01	0.93
1448890_at		KLF2	Kruppel-like factor 2 (lung)	Nucleus	transcription regulator		2.06E-05	0.40	6.59E-02	0.92	1.27E-01	0.93	3.04E-03	0.79	1.66E-02	0.88
1452016_at		ALOX5AP	arachidonate 5-lipoxygenase-activating protein	Plasma Membrane	other		2.01E-05	0.40	4.69E-01	0.98	8.09E-01	1.00	2.60E-02	0.94	1.97E-01	0.96
1427075_s_at	Duplicate Gene Syn	PCMTD2	protein-L-isoaspartate (D-aspartate) O-methyltransferase domain containing 2	Cytoplasm	enzyme		1.17E-04	0.40	5.23E-01	0.95	9.82E-01	1.00	4.83E-02	0.80	2.10E-01	1.13
1448985_at		DUSP22	dual specificity phosphatase 22	Cytoplasm	phosphatase		1.38E-03	0.39	2.07E-01	0.95	4.56E-01	0.97	6.34E-01	0.96	4.05E-01	0.96

							Stimulation Only		Compound Only				Stimulation and Compound			
Probe Set Description							CpG vs. Medium		0.25 uM E6446 vs. Medium		1.25 uM E6446 vs. Medium		CpG + 0.25 uM E6446 vs. Medium		CpG + 1.25 uM E6446 vs. Medium	
1420980_at	Duplicate Gene Syn	PAK1	p21 protein (Cdc42/Rac)-activated kinase 1	Cytoplasm	kinase		2.72E-05	0.39	3.57E-01	1.03	9.39E-01	1.00	2.96E-01	0.96	3.05E-01	1.04
1416007_at	Duplicate Gene Syn	SATB1	SATB homeobox 1	Nucleus	transcription regulator		2.21E-05	0.39	9.51E-01	1.00	2.96E-01	0.96	2.58E-01	0.91	5.69E-01	1.03
1448364_at	Duplicate Gene Syn	CCNG2	cyclin G2	Nucleus	other		3.79E-06	0.39	5.75E-01	0.98	9.01E-01	1.01	3.61E-01	0.97	8.16E-01	1.01
1416827_at		TBXAS1	thromboxane A synthase 1 (platelet)	Plasma Membrane	enzyme	ridogrel	2.64E-05	0.39	5.53E-01	0.99	2.14E-01	0.97	2.77E-02	0.88	8.90E-02	0.95
1424029_at		TSPYL4	TSPY-like 4	Nucleus	other		8.98E-05	0.39	1.81E-01	0.91	4.98E-01	0.98	7.41E-02	0.93	2.47E-01	0.94
1420699_at		CLEC7A	C-type lectin domain family 7, member A	Plasma Membrane	transmembrane receptor		4.54E-05	0.39	1.39E-02	0.92	3.78E-02	0.94	8.46E-01	0.99	9.07E-01	1.00
1416759_at	Duplicate Gene Syn	MICAL1	microtubule associated monooxygenase, calponin and LIM domain containing 1	Cytoplasm	enzyme		3.40E-05	0.39	4.49E-01	0.96	5.57E-01	0.96	7.45E-01	0.98	6.49E-01	1.03
1423924_s_at		TSPAN14	tetraspanin 14	unknown	other		5.00E-05	0.39	7.09E-01	0.98	7.73E-01	1.02	4.68E-02	0.88	6.81E-01	1.02
1415996_at	Duplicate Gene Syn	TXNIP	thioredoxin interacting protein	Cytoplasm	other		1.19E-06	0.39	5.55E-01	0.98	4.86E-02	0.94	3.04E-02	0.91	7.45E-01	0.99
1448076_at		CTR9	Ctr9, Paf1/RNA polymerase II complex component, homolog (S. cerevisiae)	Nucleus	other		5.77E-05	0.38	4.18E-01	1.08	3.39E-01	1.06	7.44E-01	0.98	3.26E-02	1.30
1417533_a_at	Duplicate Gene Syn	ITGB5	integrin, beta 5	Plasma Membrane	other	EMD121974	4.31E-05	0.38	7.24E-01	0.99	4.75E-01	0.95	4.69E-03	0.84	1.32E-01	0.94
1448546_at	Duplicate Gene Syn	RASSF3	Ras association (RalGDS/AF-6) domain family member 3	unknown	other		2.01E-04	0.38	1.91E-01	1.02	2.86E-03	0.96	4.03E-02	0.92	7.34E-01	0.99
1456439_x_at	Duplicate Gene Syn	MICAL1	microtubule associated monooxygenase, calponin and LIM domain containing 1	Cytoplasm	enzyme		6.87E-05	0.38	1.96E-01	0.96	8.60E-01	1.01	6.99E-01	0.99	7.08E-01	1.01
1420498_a_at		DAB2	Dab, mitogen-responsive phosphoprotein, homolog 2 (Drosophila)	Plasma Membrane	other		1.51E-05	0.38	6.96E-01	0.98	4.84E-01	0.96	2.27E-01	0.93	8.64E-01	1.01
1432143_a_at	Duplicate Gene Syn	HBP1	HMG-box transcription factor 1	Nucleus	transcription regulator		1.47E-04	0.38	9.04E-01	1.01	6.42E-01	1.02	1.62E-01	0.90	9.41E-01	1.00
1422527_at		HLA-DMA	major histocompatibility complex, class II, DM alpha	Plasma Membrane	transmembrane receptor		5.54E-05	0.38	4.26E-01	0.98	3.04E-01	0.97	2.97E-01	0.97	3.15E-02	0.93
1420249_s_at	Duplicate Gene Syn	Ccl6	chemokine (C-C motif) ligand 6	Extracellular Space	cytokine		2.49E-05	0.38	1.32E-01	0.92	1.40E-01	0.91	1.16E-02	0.77	4.64E-02	0.90
1426562_a_at	Duplicate Gene Syn	OLFM1	olfactomedin 1	Cytoplasm	other		1.12E-04	0.38	1.27E-01	0.90	1.98E-01	0.92	1.59E-01	0.90	1.92E-01	0.91
1419711_at		CD7	CD7 molecule	Plasma Membrane	other		1.04E-04	0.38	7.74E-01	0.99	8.13E-01	1.01	5.35E-01	0.97	4.73E-01	0.97
1416029_at		KLF10	Kruppel-like factor 10	Nucleus	transcription regulator		9.12E-05	0.37	8.83E-01	0.99	6.75E-01	0.97	1.42E-01	0.88	9.65E-01	1.00
1415997_at	Duplicate Gene Syn	TXNIP	thioredoxin interacting protein	Cytoplasm	other		7.65E-05	0.37	5.74E-01	0.96	1.85E-01	0.90	2.93E-01	0.92	3.38E-01	0.90
1416714_at	Duplicate Gene Syn	IRF8	interferon regulatory factor 8	Nucleus	transcription regulator		5.15E-05	0.37	9.99E-01	1.00	9.72E-01	1.00	3.96E-01	0.95	2.38E-01	1.09
1419609_at		CCR1	chemokine (C-C motif) receptor 1	Plasma Membrane	G-protein coupled receptor		8.58E-06	0.37	7.59E-01	0.99	4.14E-01	1.05	2.12E-01	0.92	8.01E-01	1.01
1415743_at		HDAC5	histone deacetylase 5	Nucleus	transcription regulator	tributyrin, belinostat, pyroxamide, vorinostat, romidepsin	2.02E-04	0.37	4.39E-01	0.95	4.59E-01	0.95	1.47E-01	0.90	9.41E-01	1.00
1450881_s_at	Duplicate Gene Syn	GPR137B	G protein-coupled receptor 137B	Plasma Membrane	other		1.38E-04	0.37	4.41E-05	1.15	2.03E-03	1.17	1.76E-01	0.95	3.76E-03	1.16
1448407_at	Duplicate Gene Syn	C10orf54	chromosome 10 open reading frame 54	unknown	other		3.71E-04	0.37	3.84E-01	0.96	6.39E-01	0.98	1.07E-03	0.80	1.87E-01	0.93
1416635_at		SMPDL3A	sphingomyelin phosphodiesterase, acid-like 3A	Extracellular Space	enzyme		1.74E-04	0.37	3.88E-01	0.96	8.21E-01	0.99	2.32E-03	0.77	3.83E-01	0.96
1438705_at	Duplicate Gene Syn	CBFA2T3	core-binding factor, runt domain, alpha subunit 2; translocated to, 3	Nucleus	transcription regulator		5.36E-05	0.37	3.35E-01	0.96	1.73E-01	0.96	1.84E-02	0.90	1.60E-01	0.94
1426567_a_at	Duplicate Gene Syn	PQLC1	PQ loop repeat containing 1	unknown	other		7.29E-05	0.37	4.29E-01	0.96	4.68E-01	0.97	5.70E-02	0.89	6.53E-01	0.98
1439256_x_at		Gpr137b-ps	G protein-coupled receptor 137B, pseudogene	unknown	other		3.66E-05	0.36	2.17E-01	1.05	1.46E-01	1.07	2.16E-02	0.87	3.43E-01	1.05
1450966_at		CROT	carnitine O-octanoyltransferase	Cytoplasm	enzyme		3.13E-05	0.36	1.19E-01	0.92	3.57E-01	0.95	3.03E-02	0.82	7.96E-01	0.98
1428669_at		Bmyc	brain expressed myelocytomatosis oncogene	Nucleus	other		5.36E-06	0.36	5.76E-01	0.98	3.69E-01	0.96	1.83E-02	0.89	2.83E-01	0.96
1415824_at	Duplicate Gene Syn	Scd2	stearoyl-Coenzyme A desaturase 2	Cytoplasm	enzyme		9.48E-07	0.36	6.98E-01	1.04	7.26E-01	1.03	1.32E-01	0.87	2.07E-01	0.90
1422603_at		RNASE4	ribonuclease, RNase A family, 4	Extracellular Space	enzyme		2.30E-05	0.36	8.64E-02	0.94	8.13E-01	0.99	1.76E-01	0.93	9.62E-01	1.00
1415698_at		GOLM1	golgi membrane protein 1	Cytoplasm	other		1.04E-04	0.36	8.90E-02	0.95	5.03E-01	0.98	2.71E-03	0.87	2.95E-01	0.97
1456307_s_at	Duplicate Gene Syn	ADCY7	adenylate cyclase 7	Plasma Membrane	enzyme		1.50E-05	0.36	5.69E-01	1.03	7.84E-01	0.99	4.01E-02	0.87	3.64E-01	1.06
1452050_at	Duplicate Gene Syn	CAMK1D	calcium/calmodulin-dependent protein kinase ID	Cytoplasm	kinase		1.47E-05	0.36	6.48E-01	1.01	8.67E-01	1.00	1.49E-01	0.91	2.22E-01	1.02
1455796_x_at	Duplicate Gene Syn	OLFM1	olfactomedin 1	Cytoplasm	other		9.55E-05	0.36	8.05E-01	0.98	3.37E-01	0.93	2.03E-01	0.85	3.69E-01	0.94
1423704_at		PLA2G15	phospholipase A2, group XV	Cytoplasm	enzyme		1.13E-05	0.36	9.68E-01	1.00	6.10E-01	0.98	6.93E-02	0.84	7.45E-01	0.99
1425784_a_at	Duplicate Gene Syn	OLFM1	olfactomedin 1	Cytoplasm	other		1.03E-05	0.36	1.59E-01	0.96	2.68E-01	0.94	1.10E-02	0.81	4.37E-03	0.87
1451989_a_at	Duplicate Gene Syn	MAPRE2	microtubule-associated protein, RP/EB family, member 2	Cytoplasm	other		2.79E-05	0.35	3.68E-01	0.97	3.49E-01	0.96	3.51E-01	0.88	2.30E-01	0.95
1448452_at	Duplicate Gene Syn	IRF8	interferon regulatory factor 8	Nucleus	transcription regulator		4.12E-05	0.35	3.76E-01	0.96	1.80E-01	0.93	2.85E-02	0.85	4.92E-02	0.87
1450070_s_at	Duplicate Gene Syn	PAK1	p21 protein (Cdc42/Rac)-activated kinase 1	Cytoplasm	kinase		3.75E-05	0.35	7.04E-01	1.01	4.40E-01	0.97	2.99E-02	0.94	3.53E-01	1.02
1425538_x_at	Duplicate Gene Syn	Ceacam1/Ceacam2	carcinoembryonic antigen related cell adhesion molecule 1	Plasma Membrane	other		4.89E-04	0.35	9.78E-01	1.00	2.19E-01	0.90	2.48E-02	0.83	7.98E-02	0.87
1416926_at		TP53INP1	tumor protein p53 inducible nuclear protein 1	Nucleus	other		4.76E-05	0.35	6.48E-01	0.98	6.90E-01	1.02	1.02E-01	0.92	4.04E-01	1.05
1423319_at		HHEX	hematopoietically expressed homeobox	Nucleus	transcription regulator		2.86E-06	0.35	1.55E-01	0.95	8.53E-01	0.99	7.42E-03	0.86	6.83E-01	0.99
1451075_s_at		CTDSP2	CTD (carboxy-terminal domain, RNA polymerase II, polypeptide A) small phosphatase 2	Nucleus	phosphatase		4.93E-07	0.35	1.91E-01	0.97	4.43E-01	0.97	1.55E-03	0.87	4.35E-02	0.95
1425215_at	Duplicate Gene Syn	FFAR2	free fatty acid receptor 2	Plasma Membrane	G-protein coupled receptor		1.10E-03	0.35	4.09E-01	0.96	3.92E-02	0.95	3.82E-01	0.97	5.18E-03	0.85
1455065_x_at							2.17E-05	0.35	6.32E-01	0.98	8.23E-01	0.98	1.13E-01	0.82	8.44E-01	0.98
1426389_at	Duplicate Gene Syn	CAMK1D	calcium/calmodulin-dependent protein kinase ID	Cytoplasm	kinase		8.81E-05	0.35	1.68E-01	0.94	1.67E-01	0.94	1.81E-01	0.90	9.36E-01	1.00
1448960_at	Duplicate Gene Syn	CXXC5	CXXC finger protein 5	unknown	other		8.82E-05	0.34	6.35E-01	0.97	7.86E-01	1.03	3.95E-01	0.93	6.87E-01	1.03
1450435_at		L1CAM	L1 cell adhesion molecule	Plasma Membrane	other		2.56E-04	0.34	8.35E-01	1.01	3.97E-01	0.95	5.94E-01	0.97	4.92E-01	1.03
1450065_at	Duplicate Gene Syn	ADCY7	adenylate cyclase 7	Plasma Membrane	enzyme		2.87E-06	0.34	5.47E-01	1.02	6.39E-01	1.02	1.86E-01	0.97	9.23E-02	1.10
1450967_at		PTPLAD2	protein tyrosine phosphatase-like A domain containing 2	unknown	other		1.44E-05	0.34	7.09E-01	1.02	8.69E-01	1.01	1.88E-02	0.87	8.53E-01	0.99
1424163_at		RMND5B	required for meiotic nuclear division 5 homolog B (S. cerevisiae)	unknown	other		2.93E-04	0.34	7.04E-01	0.98	8.32E-01	0.99	1.68E-02	0.84	2.68E-01	0.95
1455826_a_at		BACE1	beta-site APP-cleaving enzyme 1	Cytoplasm	peptidase		8.44E-05	0.34	7.23E-01	0.97	1.62E-01	0.90	5.51E-02	0.81	3.28E-01	0.93
1420818_at	Duplicate Gene Syn	SLA	Src-like-adaptor	Plasma Membrane	other		8.36E-05	0.34	7.12E-01	1.03	9.50E-01	1.00	2.37E-01	0.93	5.81E-01	0.96
1418394_a_at		CD97	CD97 molecule	Plasma Membrane	G-protein coupled receptor		2.34E-05	0.34	5.41E-01	0.97	4.16E-01	0.95	1.23E-02	0.79	3.80E-01	0.95
1439255_s_at	Duplicate Gene Syn	GPR137B	G protein-coupled receptor 137B	Plasma Membrane	other		1.71E-04	0.34	3.26E-01	1.08	1.51E-01	1.08	1.83E-01	0.90	7.81E-02	1.11
1423297_at	Duplicate Gene Syn	ADD3	adducin 3 (gamma)	Cytoplasm	other		8.34E-07	0.33	1.47E-01	1.04	8.64E-01	1.01	4.04E-02	0.91	1.06E-01	1.03
1449366_at		MMP8	matrix metallopeptidase 8 (neutrophil collagenase)	Extracellular Space	peptidase	marimastat	6.32E-05	0.33	6.93E-01	1.02	7.69E-01	1.01	4.11E-01	0.95	3.72E-02	1.08
1416101_a_at	Duplicate Gene Syn	HIST1H1C	histone cluster 1, H1c	Nucleus	other		5.06E-05	0.33	5.05E-03	0.85	3.94E-03	0.81	6.29E-03	0.86	5.50E-04	0.80
1415850_at		RASA3	RAS p21 protein activator 3	Plasma Membrane	ion channel		4.42E-06	0.33	3.51E-01	0.97	7.28E-01	0.98	4.05E-03	0.83	5.98E-01	0.98
1460367_at	Duplicate Gene Syn	HBP1	HMG-box transcription factor 1	Nucleus	transcription regulator		1.98E-06	0.33	2.84E-01	1.03	2.36E-01	1.05	5.20E-02	0.93	2.05E-01	1.06
1452416_at		IL6R	interleukin 6 receptor	Plasma Membrane	transmembrane receptor	tocilizumab	9.08E-05	0.33	9.17E-01	1.01	8.70E-01	1.01	5.53E-01	0.95	5.97E-01	0.97
1428790_at	Duplicate Gene Syn	NFAM1	NFAT activating protein with ITAM motif 1	Plasma Membrane	transmembrane receptor		5.17E-05	0.33	7.09E-01	1.01	2.36E-01	0.94	1.05E-04	0.90	7.70E-03	0.94
1416488_at	Duplicate Gene Syn	CCNG2	cyclin G2	Nucleus	other		6.37E-06	0.32	8.45E-01	0.99	6.23E-01	1.02	2.58E-01	0.95	7.65E-01	1.01
1418982_at		CEBPA	CCAAT/enhancer binding protein (C/EBP), alpha	Nucleus	transcription regulator		9.73E-05	0.32	5.56E-01	1.03	8.83E-01	1.01	6.62E-03	0.83	1.95E-01	0.95
1436781_at		MAN2B1	mannosidase, alpha, class 2B, member 1	Cytoplasm	enzyme		4.14E-05	0.32	7.51E-01	1.02	7.76E-01	0.98	2.53E-01	0.90	4.31E-01	1.05
1416701_at	Duplicate Gene Syn	RND3	Rho family GTPase 3	Cytoplasm	enzyme		2.60E-03	0.32	6.25E-01	0.92	7.00E-01	0.91	6.32E-01	0.92	2.60E-01	0.80
1431469_a_at	Duplicate Gene Syn	CXXC5	CXXC finger protein 5	unknown	other		3.97E-05	0.32	1.22E-01	1.04	3.24E-01	1.09	8.69E-02	0.90	2.94E-01	0.96
1423298_at	Duplicate Gene Syn	ADD3	adducin 3 (gamma)	Cytoplasm	other		3.14E-05	0.31	5.78E-01	0.97	6.21E-01	0.97	5.67E-02	0.83	9.29E-01	0.99

Probe Set Description							Stimulation Only		Compound Only				Stimulation and Compound			
							CpG vs. Medium		0.25 uM E6446 vs. Medium		1.25 uM E6446 vs. Medium		CpG + 0.25 uM E6446 vs. Medium		CpG + 1.25 uM E6446 vs. Medium	
1456195_x_at	Duplicate Gene Syn	ITGB5	integrin, beta 5	Plasma Membrane	other	EMD121974	5.75E-05	0.31	3.94E-01	0.98	1.02E-01	0.95	1.06E-03	0.82	8.74E-01	1.01
1417218_at		CALHM2	calcium homeostasis modulator 2	unknown	other		7.89E-07	0.31	6.11E-01	1.01	2.32E-01	0.96	1.37E-03	0.82	1.90E-01	0.97
1426574_a_at	Duplicate Gene Syn	ADD3	adducin 3 (gamma)	Cytoplasm	other		9.24E-06	0.31	7.31E-01	1.02	3.09E-01	0.94	9.15E-03	0.82	1.24E-01	0.91
1416978_at		FCGRT	Fc fragment of IgG, receptor, transporter, alpha	Plasma Membrane	transmembrane receptor		2.29E-05	0.31	2.41E-01	0.93	1.26E-01	0.91	6.44E-02	0.87	4.30E-02	0.85
1425216_at	Duplicate Gene Syn	FFAR2	free fatty acid receptor 2	Plasma Membrane	G-protein coupled receptor		5.30E-06	0.31	2.04E-02	0.92	8.51E-03	0.95	1.17E-04	0.95	9.56E-04	0.89
1422645_at		HFE	hemochromatosis	Plasma Membrane	transmembrane receptor		1.48E-05	0.31	4.84E-01	0.96	6.80E-02	0.91	6.38E-03	0.83	2.57E-01	0.95
1448620_at		FCGR2A	Fc fragment of IgG, low affinity IIa, receptor (CD32)	Plasma Membrane	transmembrane receptor		2.14E-05	0.31	5.04E-02	1.12	8.31E-02	1.08	1.05E-02	0.83	4.15E-01	1.04
1417391_a_at		IL16	interleukin 16	Extracellular Space	cytokine		4.18E-05	0.30	6.78E-02	0.95	1.21E-01	0.95	3.79E-02	0.94	6.39E-02	0.95
1436512_at		ARL4C	ADP-ribosylation factor-like 4C	Nucleus	enzyme		5.33E-05	0.30	3.53E-01	1.05	7.69E-01	0.98	5.97E-03	0.85	3.71E-02	0.91
1436994_a_at	Duplicate Gene Syn	HIST1H1C	histone cluster 1, H1c	Nucleus	other		2.43E-05	0.30	7.57E-02	0.83	7.05E-03	0.78	3.62E-02	0.76	3.57E-02	0.85
1427347_s_at		TUBB2A	tubulin, beta 2A class IIa	Cytoplasm	other	epothilone B, ixabepilone, colchicine,probenecid, XRP9881, ABT-751, eribulin, MST-997, AL 108, EC145, NPI-2358, milataxel, TPI 287, TTI-237, brentuximab vedotin, cabazitaxel, BMS-275183, docetaxel, vinflunine, vinorelbine, vincristine, vinblastine, paclitaxel, podophyllotoxin, colchicine	2.87E-07	0.30	5.45E-02	0.96	8.63E-02	0.95	9.25E-03	0.73	1.37E-02	0.90
AFFX-18SRNAMur/X		Rn18s	18S ribosomal RNA	unknown	other		3.47E-02	0.30	6.55E-01	0.65	8.15E-01	0.82	3.53E-01	0.47	2.34E-02	0.21
1416700_at	Duplicate Gene Syn	RND3	Rho family GTPase 3	Cytoplasm	enzyme		7.14E-05	0.29	4.42E-01	0.93	5.75E-01	0.94	1.46E-01	0.86	6.84E-02	0.85
1420819_at	Duplicate Gene Syn	SLA	Src-like-adaptor	Plasma Membrane	other		2.93E-05	0.29	2.97E-01	1.05	8.36E-01	0.99	6.42E-02	0.91	5.24E-01	1.03
1419247_at	Duplicate Gene Syn	RGS2	regulator of G-protein signaling 2, 24kDa	Nucleus	other		2.55E-05	0.29	9.28E-01	1.00	2.95E-01	0.94	1.40E-02	0.82	1.34E-01	0.93
1426624_a_at		YPEL3	yippee-like 3 (Drosophila)	unknown	other		5.92E-05	0.28	5.41E-01	0.96	5.67E-01	0.97	2.04E-02	0.83	1.77E-01	0.92
1434034_at		CERK	ceramide kinase	Plasma Membrane	kinase		7.85E-06	0.28	5.50E-01	0.97	8.01E-01	0.99	2.67E-04	0.82	4.03E-02	0.95
1419248_at	Duplicate Gene Syn	RGS2	regulator of G-protein signaling 2, 24kDa	Nucleus	other		7.30E-06	0.28	5.02E-01	1.01	2.42E-01	0.96	2.27E-02	0.85	5.25E-01	0.98
1425714_a_at	Duplicate Gene Syn	NFAM1	NFAT activating protein with ITAM motif 1	Plasma Membrane	transmembrane receptor		1.69E-05	0.28	3.78E-01	1.06	8.70E-01	1.01	7.79E-01	0.97	5.28E-01	1.04
1434378_a_at		MXD4	MAX dimerization protein 4	Nucleus	transcription regulator		6.86E-05	0.27	9.96E-01	1.00	4.66E-01	1.05	1.97E-02	0.84	6.13E-01	0.97
1417128_at		PLEKHO1	pleckstrin homology domain containing, family O member 1	Plasma Membrane	other		3.82E-06	0.27	3.63E-01	0.96	5.36E-01	1.02	9.04E-01	0.99	1.21E-01	1.08
1448710_at		CXCR4	chemokine (C-X-C motif) receptor 4	Plasma Membrane	G-protein coupled receptor	plerixafor	3.53E-06	0.27	4.95E-01	1.03	6.99E-01	0.98	2.87E-02	0.86	6.43E-02	1.02
1418553_at		ARHGEF18	Rho/Rac guanine nucleotide exchange factor (GEF) 18	Cytoplasm	other		1.29E-06	0.27	2.40E-01	1.04	4.62E-01	1.06	3.93E-01	0.97	1.59E-01	1.06
1430125_s_at	Duplicate Gene Syn	POLC1	POL loop repeat containing 1	unknown	other		7.51E-06	0.26	9.30E-01	1.00	8.79E-01	0.99	2.07E-02	0.84	3.23E-01	0.95
1437463_x_at	Duplicate Gene Syn	TGFBI	transforming growth factor, beta-induced, 68kDa	Extracellular Space	other		3.53E-05	0.26	5.40E-01	1.03	9.38E-01	1.00	3.23E-02	0.86	1.15E-01	0.92
1428578_s_at		Ppfia4	protein tyrosine phosphatase, receptor type, f polypeptide (PTPRF), interacting protein (liprin), alpha 4	unknown	other		5.05E-08	0.26	1.43E-02	0.94	7.89E-03	0.94	7.31E-03	0.86	1.77E-02	0.92
1437626_at		ZFP36L2	ZFP36 ring finger protein-like 2	Nucleus	transcription regulator		2.62E-07	0.26	3.95E-01	0.98	2.60E-01	1.01	4.83E-02	0.97	5.62E-02	1.05
1415871_at	Duplicate Gene Syn	TGFBI	transforming growth factor, beta-induced, 68kDa	Extracellular Space	other		8.39E-06	0.26	6.94E-01	0.99	1.73E-01	0.98	3.09E-03	0.84	5.08E-04	0.90
1448123_s_at	Duplicate Gene Syn	TGFBI	transforming growth factor, beta-induced, 68kDa	Extracellular Space	other		3.68E-06	0.25	8.06E-01	0.99	4.71E-01	0.96	1.16E-02	0.84	1.75E-01	0.94
1456250_x_at	Duplicate Gene Syn	TGFBI	transforming growth factor, beta-induced, 68kDa	Extracellular Space	other		1.73E-05	0.25	8.05E-01	1.01	8.52E-01	0.99	6.67E-02	0.84	6.14E-01	0.97
1451344_at		TMEM119	transmembrane protein 119	Cytoplasm	other		2.11E-05	0.24	5.74E-01	0.98	7.92E-01	0.99	8.12E-03	0.89	2.38E-01	0.97
1435375_at		FAM105A	family with sequence similarity 105, member A	unknown	other		1.95E-08	0.24	4.29E-01	1.04	1.13E-01	1.03	1.77E-01	0.96	6.06E-01	0.99
1420895_at		TGFBR1	transforming growth factor, beta receptor 1	Plasma Membrane	kinase		2.66E-05	0.24	3.15E-01	0.96	1.46E-01	1.04	1.08E-01	0.87	4.48E-01	1.04
1454858_x_at	Duplicate Gene Syn	METTL7A	methyltransferase like 7A	unknown	other		1.27E-04	0.23	5.76E-01	1.07	3.31E-01	1.12	7.55E-01	0.97	4.03E-01	1.10
1451486_at		SLC46A3	solute carrier family 46, member 3	Extracellular Space	other		2.26E-04	0.23	4.50E-01	0.98	2.07E-01	0.94	8.35E-01	1.01	6.11E-02	0.95
1417590_at		CYP27A1	cytochrome P450, family 27, subfamily A, polypeptide 1	Cytoplasm	enzyme		1.51E-03	0.23	2.88E-01	0.96	4.96E-01	1.06	1.95E-02	0.82	5.37E-02	1.11
1419768_at		CD22	CD22 molecule	Plasma Membrane	transmembrane receptor	epratuzumab, BL22 immunotoxin, inotuzumab ozogamicin, combotox, RFB4-dgRTA	5.67E-04	0.23	3.43E-01	0.96	2.23E-01	0.94	5.00E-02	0.91	7.23E-01	0.98
1416617_at		ACSS1	acyl-CoA synthetase short-chain family member 1	Cytoplasm	enzyme		5.88E-05	0.22	4.79E-01	0.96	1.75E-01	0.91	4.05E-02	0.86	3.12E-01	1.07
1425281_a_at		TSC22D3	TSC22 domain family, member 3	Nucleus	transcription regulator		3.61E-04	0.21	4.86E-01	0.90	7.41E-01	0.95	7.55E-02	0.76	2.75E-01	0.87
1428306_at		DDIT4	DNA-damage-inducible transcript 4	Cytoplasm	other		1.71E-06	0.20	8.15E-01	0.99	6.89E-01	1.02	2.92E-02	0.82	4.23E-01	1.05
1424975_at		Siglec5	sialic acid binding Ig-like lectin 5	Plasma Membrane	other		2.71E-05	0.20	7.87E-01	1.02	3.31E-01	0.95	8.69E-01	0.99	1.72E-01	1.08
1416619_at	Duplicate Gene Syn	C10orf54	chromosome 10 open reading frame 54	unknown	other		2.44E-07	0.20	2.73E-01	0.93	6.06E-01	0.96	1.15E-02	0.81	4.94E-01	0.97
1450357_a_at		CCR6	chemokine (C-C motif) receptor 6	Plasma Membrane	G-protein coupled receptor		1.26E-04	0.19	2.62E-01	0.97	9.16E-01	1.00	8.85E-01	0.99	9.09E-01	1.00
1454984_at		LIFR	leukemia inhibitory factor receptor alpha	Plasma Membrane	transmembrane receptor		1.48E-05	0.19	2.90E-01	1.05	4.23E-01	0.97	5.62E-02	0.80	4.08E-01	1.10
1425214_at		P2RY6	pyrimidinergic receptor P2Y, G-protein coupled, 6	Plasma Membrane	G-protein coupled receptor		4.65E-04	0.19	9.20E-01	1.00	5.43E-01	0.97	6.92E-01	0.98	6.64E-01	1.03
1434151_at	Duplicate Gene Syn	METTL7A	methyltransferase like 7A	unknown	other		2.91E-05	0.19	7.41E-01	0.99	1.59E-01	1.05	1.72E-02	0.84	3.61E-01	0.96
1434150_a_at		Mettl7a2/Mettl7a3	methyltransferase like 7A3	unknown	other		6.46E-05	0.18	9.45E-01	0.99	9.27E-01	1.01	1.76E-01	0.85	7.18E-01	1.04
1424383_at		TMEM51	transmembrane protein 51	unknown	other		6.44E-07	0.18	8.56E-01	0.99	1.07E-01	1.02	1.01E-02	0.83	2.38E-02	0.96
1453474_at		ABHD15	abhydrolase domain containing 15	Extracellular Space	other		6.30E-05	0.18	9.31E-01	1.00	3.62E-01	1.01	3.10E-03	0.80	3.74E-01	0.97
1417395_at	Duplicate Gene Syn	KLF4	Kruppel-like factor 4 (gut)	Nucleus	transcription regulator		9.59E-05	0.17	6.67E-01	0.97	1.10E-01	0.92	3.90E-03	0.78	1.42E-01	0.87
1448747_at		FBXO32	F-box protein 32	Cytoplasm	enzyme		3.39E-05	0.16	4.47E-01	1.08	5.82E-01	0.96	1.12E-02	0.68	1.76E-02	0.73
1417394_at	Duplicate Gene Syn	KLF4	Kruppel-like factor 4 (gut)	Nucleus	transcription regulator		6.11E-06	0.06	5.21E-01	0.95	1.94E-01	0.91	6.81E-02	0.79	9.20E-01	0.99