July 2, 2014

VIA HAND DELIVERY

Dockets Management Branch, HFA-305
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Citizen Petition Requesting That FDA Refrain From Approving Any Abbreviated New Drug Application Referencing Copaxone® (glatiramer acetate injection) Until Certain Conditions Are Met

Dear Sir or Madam:

On behalf of Teva Pharmaceutical Industries Ltd., Teva Neuroscience, Inc. ("Teva")[1] hereby submits this Citizen Petition pursuant to 21 C.F.R. § 10.30 and sections 505(j) and 505(q) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. §§ 355(j) and 355(q). For the reasons that follow, Teva respectfully requests that the Commissioner of Food and Drugs consider the scientific information submitted in this Petition and refrain from approving any abbreviated new drug application ("ANDA") that references Copaxone® (glatiramer acetate injection) unless and until the conditions specified in this Petition are satisfied to assure that follow-on products are safe and effective. Teva manufactures and distributes Copaxone®, a treatment for the reduction of frequency of relapses in relapsing-remitting multiple sclerosis ("RRMS").

This Petition is submitted following guidance from the Food and Drug Administration ("FDA" or "the Agency") in the letter dated June 9, 2014 (attached hereto as Exhibit 1). In the letter, the Agency asks that Teva make public through the citizen petition process information submitted on May 23, 2014 as an amendment and general correspondence concerning the New Drug Application ("NDA") for Copaxone® (NDA 20-622). Teva is providing herein all information from the May 23, 2014 submission, as well as additional findings from Teva's

[1] Teva Pharmaceutical Industries Ltd. is a global pharmaceutical company specializing in the development, production, and marketing of generic, proprietary, and branded pharmaceuticals, and active pharmaceutical ingredients. Teva is among the top 20 pharmaceutical companies and is the leading generic pharmaceutical company in the world. Teva Neuroscience is the branded neurological products subsidiary of Teva Pharmaceutical Industries Ltd. and is responsible for the clinical development, registration, and marketing of Teva's branded neurological products in North America, including Copaxone®.

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ongoing research. Teva continues to study Copaxone® and other glatiramoids, publishing the findings as rapidly as possible in the peer-reviewed literature in order to advance scientific understanding of these complex medicines, and ensure the safe and efficacious treatment of multiple sclerosis ("MS") patients worldwide.

I. Actions Requested

Copaxone® is a non-biologic complex drug ("NBCD") and first-generation nanomedicine composed of an uncharacterized mixture of immunogenic polypeptides in a colloidal suspension. The active ingredient in Copaxone® – glatiramer acetate – is not a single molecular entity but rather a heterogeneous mixture of potentially millions of distinct, synthetic polypeptides of varying lengths, some containing up to 200 amino acids, with structural complexity comparable to that of proteins. The complexity of glatiramer acetate is amplified by the fact that its exact mechanisms of action are unknown, and the specific amino acid sequences (epitopes) responsible for its efficacy and safety cannot be identified. Accordingly, like many biological products, glatiramer acetate is defined, in large part, by its well-controlled manufacturing process, which has been used by Teva for more than twenty years.

As part of its ongoing commitment to better characterize Copaxone®, Teva continues to evaluate the physicochemical and biological properties of Copaxone® using state-of-the-art technology. In a prior Petition, Teva submitted the results of new gene expression studies comparing Copaxone® and purported, foreign, generic glatiramer acetate products.[2] Those studies produced multiple lines of evidence suggesting that purported "generic" products have a significantly more variable biological impact than Copaxone®, particularly with respect to immune cells associated with inflammatory response and beneficial tolerance. The results from these recent tests thus raise significant concerns that proposed generic products manufactured via different processes and using different starting materials may have undetected structural and compositional differences from Copaxone® that could compromise safety, immunogenicity, and effectiveness.

In its May 2, 2014, response to Teva's most recent Petition, FDA expressed interest in ongoing research conducted by Teva and others, stating that "FDA continues to actively consider the issues you have raised and the information you have included in your Petition" and that "scientific information regarding this complex drug continues to accumulate, which in turn means that FDA continues to update the information available to it … ".[3] FDA also noted that some specific details associated with the gene expression studies conducted by Teva in order to characterize similarities and differences between Copaxone® and purported "generics" were missing from the Petition. These include references that characterize the genetic pathways postulated, documentation of those pathways themselves, in-depth analysis of the 98 genes

[2] *See* Docket No. FDA-2013-P-1641 (Dec. 5, 2013) (Exhibit 2). In an earlier petition, Teva submitted the results of traditional colloidal assessment experiments to confirm that Copaxone® is a colloidal suspension rather than a true solution. *See* Docket No. FDA-2013-P-1128 (Sept. 12, 2013) (Exhibit 3).

[3] FDA Response to Sixth Copaxone Petition, FDA-2013-P-1641, pp. 5-6 (note20) (May 2, 2014) (Exhibit 4).

identified, and additional evidence that the observed differences are clinically significant to the treatment of MS patients.

Some of the Agency's feedback has been addressed by recent material provided by Teva and deposited by the FDA under the same docket, including Teva's peer-reviewed publication in PLOS ONE,[4] as well as the briefing document and powerpoint slides shared with the FDA in a Type C Meeting that took place on February 25, 2014.[5] These documents outline in detail the experimental design, analytical approach and the clinical relevance associated with the gene expression studies pursued by Teva. In order to address the specific feedback from the Agency, provide the latest findings (including investigations conducted further to the May 23 NDA submission), and allow FDA an in-depth review of the methodology and full set of results, this document summarizes the available data gathered to date by Teva and analyzed by Immuneering Corporation.[6]

In brief, as part of Teva's ongoing commitment to better understand Copaxone®, Teva studied its effect at the ***level of gene expression across the entire genome*** (unbiased, without prior hypothesis about the genes for which expression pattern may be altered and without choosing which genes to focus on or study) in a variety of immunologically relevant model systems, including mouse splenocytes, human monocytes, and peripheral blood mononucleated cells ("PBMCs") from MS patients. **The genome-wide approach is critical, because two glatiramoids can appear identical based on a small panel of genes, yet differ significantly in their impact on other genes that are potentially highly relevant to safety and/or efficacy** (as illustrated in Section II.B below and on slides 49-50 of the powerpoint presentation at the February 25, 2014 Type C meeting (Exhibit 6)). **Using multiple model systems is equally critical, since acting as an antigen, Copaxone® significantly impacts a variety of immunological cell types**. The unbiased approach allows identification of genes and pathways with subtle, yet robust, differential expression patterns following stimulation by different glatiramoids in different experimental contexts. The functionality of identified genes and pathways is then described based on experimental data reported in the peer-reviewed literature. As described below, the research has also shown that various model systems capture different aspects of Copaxone®'s mechanism of action, such that no single cell type or system tested was sufficient to fully characterize the biological impact of this medicine.

The core analysis methods used for these studies are validated and considered standard in the field (experimental design methodologies: Churchill, Nat. Genet., 2002; microarray data normalization method: Quackenbush, Nat. Genet., 2002; batch correction methodology: Johnson et al, Biostat, 2007; differential expression methodology: Smyth, Stat Appl Genet Mol Biol.,

[4] Towfic, F. et al. Comparing the Biological Impact of Glatiramer Acetate with the Biological Impact of a Generic. PLOS ONE. (Jan. 8, 2014) (Exhibit 5).

[5] Teva Presentation at FDA Type C Meeting (Feb. 25, 2014) (Exhibit 6).

[6] This submission also addresses comments filed to the prior docket (Docket No. FDA-2013-P-1641) by Mylan Pharmaceuticals, Inc. dated April 29, 2014, which (a) dismisses potential safety issues and batch-to-batch manufacturing variability identified in a similar product from the company Mylan selected to manufacture the API for their ANDA, and (b) raises inaccurate and outdated objections to an older subset of Teva's scientific communications. For completion, a detailed response to this comment is supplied in Appendix 3.

2004). Novel, innovative approaches were developed by Immuneering Corporation so as to address particular questions, such as methods to determine enrichment for specific immunological cell types.

The null hypothesis in traditional gene-expression studies, including Teva's studies with the glatiramoids, is that there are no significant gene expression differences induced between the treatments. As such, the expectation is that regardless of the biological system used for testing, genes would show no statistically significant, nor biologically meaningful, differences among the various treatments. Only in cases where the treatments induce significant observable effects, genes differentially expressed between treatments will pass the stringent statistical tests, and false discovery rate (FDR) correction for multiple hypotheses.[7] These stringent requirements were imposed *a priori* across all tests to ensure robustness of results and minimizing of spurious findings. Such statistically significant differences, if biologically meaningful (e.g., related to the disease biology or any of the drug's known or putative targets and downstream pathways), warrant further studies, as two drugs that have identical activities in biological systems should not induce statistically observable and biologically enriched differences when compared against each other.

It should be emphasized that these studies were not designed to establish a particular set of genes in a specific model system as a panel to evaluate "sameness" between differently manufactured glatiramoids. Instead, these were designed to assess the degree of similarity in the impact of two glatiramoids on relevant biological pathways. The application of robust methodology (high number of replicates, conditions and time-points, where relevant) was aimed to describe pathways changed by different treatments out of the entire milieu of genomic patterns. The results obtained across the tested experimental models revealed statistically significant differences between glatiramoids, which were intended to be similar and to perform the same function, despite stringent statistical threshold requirements. This was noteworthy particularly in genes highly relevant to disease processes and drug response mechanisms. In addition, the differences observed revealed a complex interplay between immunological pathways, such that some differences were common to multiple systems, while many others were dependent on the specific model system (for example, some key genes modulated in T cells were not the same as in monocytes). This is not surprising for a process that involves multifaceted interactions between many immune system components, and is also exemplified in experimental studies of Copaxone®'s mechanism of action. Thus, no single model system, characterization method, or set of genes tested was sufficient to comprehensively capture the differences (or "sameness") between the drugs. These observations indicate a need for in-depth investigation of comparative gene expression profiles in several relevant pre-clinical systems as key indicators of similarity and/or sameness between generic candidates and the original drug within the context of NBCDs. Ideally, the concordance between high-resolution physicochemical measures (e.g. ion motility mass spectrometry, IMMS), gene expression profiling and clinical trials would allow a more definitive assessment of equivalence in terms of patient benefit and safety.

The challenges inherent in combining and interpreting data from the wide range of characterization methods currently available for complex drugs are well recognized in FDA's

[7] Benjamini Y, Hochberg Y (1995) Controlling the false discovery rate: a practical and powerful approach to multiple testing. Journal of the Royal Statistical Society Series B (Methodological): 289–300.

recently announced funding opportunity for a research project entitled "Development of an Integrated Mathematical Model for Comparative Characterization of Complex Molecules."[8] The Agency's announcement recognizes the need for innovative approaches, seeking the development of novel methods to "determine whether the type and number of in vitro chemical and biological characterization assays employed are sufficient to establish the sameness or similarity between the reference and follow-on (or generic) drug products for the complex molecules." Teva is in full support of the Agency's efforts in this area, and encourages exhaustive scientific research to address the important, unanswered questions described in the announcement.

The potential of biological characterization assays, such as gene expression, to yield information relevant to patient safety is exemplified most strikingly by findings from studies in a human monocyte (THP-1) cell line comparing Copaxone® with Probioglat (sold in Mexico by Probiomed), described below in section II.B.3. The tests revealed that genes significantly upregulated by Probioglat relative to Copaxone® were significantly enriched for inflammatory pathways and included key pro-inflammatory genes that could be harmful to MS patients. At the same time, Probioglat downregulated several anti-inflammatory genes, thus reducing the beneficial effects of these genes, compared to Copaxone®. Results were corroborated by gene-level, pathway-level and independent qRT-PCR analyses. These findings may provide clues to prediction of the serious clinical reports from Mexico post introduction of this purported generic to the market (January 2013). The suffering of MS patients in Mexico reflected in reports on adverse reactions and exacerbated disease progression may be due to a biological imbalance between anti-inflammatory and pro-inflammatory processes, which may be discernible in gene expression differences such as those described herein.

Teva previously has raised the above issues regarding active ingredient sameness, immunogenicity and bioequivalence with FDA in a series of Citizen Petitions dating back to 2008.[9] In its responses to Teva's prior Petitions, FDA has taken the position that it would be "premature and inappropriate" to provide a substantive decision on the approval requirements for ANDAs for glatiramer acetate while FDA is still reviewing pending applications.[10] Teva's prior Petitions thus remain largely unanswered.

On May 23, 2014, Teva submitted the new scientific evidence described above as an amendment and general correspondence to the NDA for Copaxone®. On June 9, 2014, the Agency issued a letter to Teva requesting that "if [Teva] wish[es] the Agency to consider the

[8] Available at: http://grants.nih.gov/grants/guide/rfa-files/RFA-FD-14-082.html.

[9] The prior Citizen Petitions were submitted in 2008, 2009, 2010, 2012 and 2013, respectively, and are incorporated herein by reference. *See* FDA-2008-P-0529 (Sept. 26, 2008) (Exhibit 7); FDA-2009-P-0555 (Nov. 13, 2009) (Exhibit 8); FDA-2010-P-0642 (Dec. 10, 2010) (Exhibit 9); FDA-2012-P-0555 (June 4, 2012) (Exhibit 10); FDA-2013-P-1128 (Sept. 12, 2013) (Exhibit 3); FDA-2013-P-1641 (Dec. 5, 2013) (Exhibit 2). Teva also incorporates by reference any exhibits to those petitions although, for efficiency's sake, such exhibits are not being re-submitted because they are either FDA documents that are routinely available to the public (e.g., approved labeling, guidance documents and petition responses) or recognized medical or scientific textbooks or articles that are readily available to the agency. *See* 21 C.F.R. § 10.20(c)(1)(iii), (iv).

[10] *See, e.g.*, FDA's Response to Sixth Copaxone Petition, FDA-2013-P-1641 (May 2, 2014).

information and arguments set forth in your May 23, 2014 letter and white paper, that you submit these documents as a citizen petition in accordance with section 505(q) of the FD&C Act."[11] Although Teva believes the Agency can consider the information submitted to the Copaxone® NDA outside the context of a new citizen petition, Teva nevertheless has decided to comply with the Agency's request. Accordingly, Teva is hereby renewing and supplementing the arguments made in its prior Petitions regarding active ingredient sameness, immunogenicity and bioequivalence testing and presenting new scientific data and information to support those arguments.[12] At bottom, Teva believes it would be contrary to the public health for FDA to approve a purported generic glatiramer acetate product that, based on current analytical technologies, can only be shown to be similar, rather than identical, to Copaxone® – particularly without any clinical testing whatsoever to address residual uncertainty regarding immunogenicity, bioequivalence, safety or effectiveness.

Consequently, Teva respectfully requests that the Commissioner:

1. Review and consider the new scientific data and information contained in this Petition prior to approving any ANDA that relies upon Copaxone® as the reference listed drug ("RLD"); and

2. Based upon the additional scientific information and data contained in this Petition, as well as the information and arguments set forth in Teva's prior Petitions (which are incorporated herein by reference), refrain from approving any ANDA that relies upon Copaxone® as the RLD unless and until the ANDA contains:

   a. Information demonstrating that the proposed generic product contains the *identical* active ingredient as Copaxone®, not merely an active ingredient that is similar (or even highly similar) to Copaxone®'s, including data from high-resolution physicochemical, biological and genome-wide expression methods;

   b. Results of non-clinical and clinical investigations, including in-depth analyses of comparative gene expression profiles in several relevant preclinical systems, demonstrating that the immunogenicity risks associated with the proposed generic product are no greater than the risks associated with Copaxone®, including a demonstration that the risks of alternating or switching between use of the proposed product and Copaxone® are not greater than the risks of using Copaxone® without such alternation or switching; and

[11] Letter from Nancy K. Hayes, Acting Director, Office of Regulatory Policy, CDER, FDA, to Dennis Ahern, MS, Senior Director, Regulatory Affairs, Teva Pharmaceuticals USA, at 2 (June 9, 2014) (Exhibit 1).

[12] Because this submission contains new scientific information, Teva is required to file it as a new Citizen Petition rather than as a Petition for Reconsideration. *See* 21 C.F.R. § 10.33(e).

c. Results of comparative clinical investigations in RRMS patients using relevant safety and effectiveness endpoints demonstrating that the proposed generic drug is bioequivalent to Copaxone®.

II. Statement of Grounds

A. Factual Background

1. Development of Copaxone®

In the 1960's, Israeli scientists at the Weizmann Institute were attempting to develop a synthetic copolymer that would mimic myelin basic protein, an autoantigen attacked by the immune system in MS pathoetiology, resulting in ***destruction*** of myelin. Their goal was to use the synthetic copolymer to ***induce*** an MS-like disease in animals so as to develop a model mimicking the disease and useful in evaluating possible treatment options for MS. Rather than induce the disease, however, one of the copolymers they synthesized (known as "copolymer-1") actually ***suppressed*** the disease in animals. The Weizmann scientists immediately recognized the potential of this copolymer mixture to treat MS.

Through intense development efforts in the 1980's, the Weizmann scientists finally were able to conduct a limited clinical trial of copolymer-1 in MS patients, but the results were mixed. While some patients responded favorably, others experienced local injection site reactions and, on rare occasions, adverse side effects including difficulty breathing, palpitations, severe flush, sweating, and anxiety. Since copolymer-1 was being developed for daily injection, those side effects posed a serious health hazard to prospective patients.

In November 1987, Teva partnered with Weizmann's commercial affiliate to develop copolymer-1 into a useful pharmaceutical product. Among other things, the team of scientists working on the drug eventually discovered on the basis of certain laboratory tests that the toxicity of a copolymer-1 mixture was related in part to its molecular weight: the higher the average molecular weight of the product, and the higher the percentage of high-molecular weight polypeptides in the mixture, the more likely it was to be toxic. They also discovered that at lower molecular weights, copolymer-1 mixtures were likely to remain therapeutically active. Having discovered a new lower molecular weight product with improved tolerability characteristics, Teva conducted a new clinical trial for a copolymer-1 mixture. That trial found that daily injections of copolymer-1 yielded a statistically significant reduction in relapse rates for patients with RRMS.

FDA approved Copaxone® for commercial marketing in the United States in late 1996 and it remains widely prescribed to this day. Copaxone® is "indicated for reduction of the frequency in relapses in patients with RRMS, including patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis." To be effective in the 20 mg version at issue here, patients administer the drug by subcutaneous injection (*i.e.*, under the skin, rather than into a vein or artery) every single day; tens of thousands of patients have been doing so for almost two decades.

Clinical studies and extensive experience with Copaxone® in patients diagnosed with RRMS have demonstrated its consistent therapeutic efficacy. The cumulative exposure to Copaxone® is approximately 2 million patient-years, with some patients effectively treated with Copaxone® for more than 20 consecutively years.

As FDA long has recognized, Copaxone® "is not a conventional drug, either in chemical composition or in its presumed mechanism of action."[13] Rather than consisting of a single molecular entity, Copaxone® is a heterogeneous polypeptide mixture containing millions of distinct synthetic polypeptides of varying lengths (up to an estimated 200 amino acids), sequences, and molecular weights, with a structural complexity that exceeds that of some proteins. In that respect, Copaxone® has almost nothing in common with typical small-molecule drugs like the therapeutically active ingredients in Tylenol® (acetaminophen) or Advil® (ibuprofen), where scientists have been able to map ***every atom*** of those products and ***their precise structural arrangements***. Given the lack of clear pharmacokinetic and pharmacodynamic markers and mapping of molecular structure for Copaxone®, it remains a unique sub-class within NBCDs, described as a heterogeneous mixture of polymeric molecules. Given the uncertainty in accurate characterization of Copaxone®, it is no surprise that the drug's therapeutically active components—the specific amino acid sequences (acting effectively as immunological "epitopes", or antigenic motifs that uniquely activate certain aspects of the immune system, analogous to a vaccine) responsible for its clinical efficacy—have yet to be identified.

Not only does Copaxone® remain a challenge for complete physicochemical characterization; its precise mechanism of action (i.e. the manner in which the drug exerts its therapeutic activity), and associated pharmacodynamics biomarkers, are not fully understood. Yet, intense research over almost two decades indicates both direct and indirect immunological effects, attributed to the fact that Copaxone® is an antigen. As such, it is highly immunogenic, meaning that exposure to the product generates a complex cascade of immune events that is difficult to fully characterize. Immunogenicity is generally a potential concern, because anything that impacts how the body's immune system functions has potentially significant health consequences. A delicate balance between pro- and anti-inflammation is crucial to MS pathoetiology and conversely to its successful management. It is thus particularly concerning in the case of MS patients, who have a diagnosed inflammatory immune system disorder. Copaxone® induces immune reactions that are favorable and beneficial to patients as has been consistently demonstrated over more than two decades: The product functions like a therapeutic vaccine (defined by FDA as "an immunogen, the administration of which is intended to stimulate the immune system to result in the prevention, amelioration or therapy of any disease or infection"),[14] eliciting beneficial responses in treated subjects by modulating the patient's immune system over an extended period of time. Even so, Copaxone®'s package insert warns

[13] Letter from P. Leber (former Director, Division of Neuropharmacological Drug Products) to B. Mackler (Dec. 10, 1992) (Exhibit 11).

[14] Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product, January 1999, *available at:* http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm076612.htm.

that chronic use has the potential to alter healthy immune function, as well as induce pathogenic immune mechanisms (though no such effects have been observed with Copaxone® over 2 million patient-years of exposure).

To this end, Copaxone® has been linked by the FDA to white blood (immunological) cells' function as reflected in the FDA's Division of Neurology Products recent decision to require Teva to conduct a clinical trial as a condition of approving an application for a more concentrated version of the product—one that included the **same** 20 mg of Copaxone® as the first version marketed since 1996, made using Teva's **same precise** manufacturing process and controls, but presented in 0.5 mL of water rather the 1.0 mL of water with Copaxone®'s existing formulation—**based on concerns that removing just 0.5 mL of water (half a milliliter of water!) might render the product unsafe or ineffective.**[15] Similarly, the recently approved 40 mg dosage of Copaxone® (in 1 mL, used 3 times per week) was approved based on clinical trials (i.e. GALA and GLACIER). Specifically, the GALA trial was a multinational, multicenter, randomized, parallel-group study performed in subjects with RRMS to assess the efficacy, safety and tolerability of Glatiramer Acetate ("GA") injection 40 mg administered three times a week compared to placebo in a double-blind design. A total of 1404 patients were randomized at a 2:1 ratio between active and placebo treatment arms across 17 different countries and a total of 155 recruitment centers.

Precisely because the product's chemical makeup cannot be fully characterized, carefully regulating the manufacturing process is the only way Teva can ensure that the product it produces is an unaltered and consistent Copaxone®. Teva prepares Copaxone® using a precise, well-controlled manufacturing process which results in a heterogeneous mixture of literally millions of distinct, synthetic polypeptides in a liquid colloid mixture. Teva routinely conducts extensive quality testing to ensure consistency among various batches of Copaxone®. These tests verify that each batch of Copaxone® possesses certain specific characteristics as measured by an array of proprietary and confidential specifications, including: (1) a specific molecular weight distribution profile; (2) complex reproducible patterns in its amino-acid sequences; (3) a characteristic ratio of molecules with C-terminal carboxylates to diethylamides; (4) a characteristic electrophoretic profile; (5) specific hydrophobic interactions due to unique charge dispersion; (6) a specific proteolytic digestion profile; (7) a specific affinity to glatiramer acetate antibodies; and (8) a specific potency as determined by its biorecognition by glatiramer acetate-specific T cells. The precise battery of testing protocols that Teva uses (including these and many others), and the precise specifications Teva applies in evaluating the results of those tests, is proprietary, confidential, and subject to trade-secret protection.

Despite Teva's ability to reproduce Copaxone® with consistency and efficacy over the last several decades, it bears repeating that Teva has not been able to fully characterize the drug despite extensive efforts to do so. Current analytical methods are not capable of individually separating and then fully characterizing the millions of individual polypeptides in the Copaxone®

[15] Letter from R. Katz to D. Ahern, NDA 20-622/S-077, at 1 (Dec. 21, 2010) ("The uncertainty about [Copaxone®'s] mechanism of action, and the fact that some of the effect may be related to the activation of lymphocytes in the periphery, raise questions about a possible impact of a high concentration/lower volume formulation on the safety and efficacy of the product.").

mixture. While Teva's proprietary analytical methods thus help to ensure that Teva's manufacturing process has been properly implemented by identifying potential ***differences*** between batches of Copaxone®, they cannot conclusively demonstrate that the clinically relevant polypeptide sequences in two putative versions of Copaxone® that are manufactured by different processes are ***identical*** in all material respects.

In fact, underscoring the complexity of these challenges, FDA has recently issued a request for proposals regarding this class of drugs, entitled "Development of an Integrated Mathematical Model for Comparative Characterization of Complex Molecules."[16] The Agency's initiative seeks innovative approaches for the development of novel methods to "determine whether the type and number of in vitro chemical and biological characterization assays employed are sufficient to establish the sameness or similarity between the reference and follow-on (or generic) drug products for the complex molecules." The end goal of this effort is to construct mathematical models that specifically aid in demonstrating "sameness" between a complex innovator drug (a macromolecule or heterogeneous mixture of molecules, e.g. Copaxone®) and a follow-on generic. The goal of the FDA's request is to help determine the extent to which additional pre-clinical assays or clinical studies are needed to determine similarity or sameness between the reference innovator drug and the generic drug product.

Finally, as part of Teva's ongoing commitment to better understand Copaxone®, Teva also has studied Copaxone®'s effect at the ***level of gene expression across the entire genome*** (unbiased, without prior hypothesis about the genes for which expression pattern may be altered and without choosing which genes to focus on or study). Genes encode proteins which carry out an array of biological processes in the body, including processes that are essential to the immune system response manifested by exposure to Copaxone®. So-called gene "microarray technology" allows scientists to observe which genes are "turned on" (in scientific terms, "upregulated") as well as which genes are "turned off" (in scientific terms, "downregulated") after exposure to various conditions, including stimulation by pharmaceutical products, via measuring the level of mRNA, which is the transitional phase between genes and proteins along the translation process. Teva's gene expression analysis of mouse splenocytes, as well as a human monocyte cell line (THP-1), exposed to Copaxone®, reveals favorable, upregulation of anti-inflammatory genes. These studies provide support for the vast experimental evidence that Copaxone® exerts its well-established therapeutic benefits in part by modulating the immune system to turn on beneficial genes (e.g., anti-inflammatory and neuroprotective) and turn off harmful ones (e.g., pro-inflammatory).

[16] Available at: http://grants.nih.gov/grants/guide/rfa-files/RFA-FD-14-082.html.

2. Experience With Purported Generic Versions of Copaxone® In Foreign Countries

Several competitors have sought approval to market putative generic versions of the drug in foreign countries. Although many of those jurisdictions have required applicants to conduct clinical trials as a condition of approval—and none of *those* jurisdictions has approved a generic version of Copaxone®—others have not been as careful, and those countries since have allowed purported Copaxone® generics to enter the market without proof of the equivalence of the putative generics to Copaxone®. Teva has purchased those products in the foreign marketplace, and subjected those products to a battery of tests—including both physicochemical analyses and gene expression analyses. Aspects of these studies have been described to the Agency in Teva's citizen petitions, published in peer-reviewed literature, presented at a Type C meeting (February 25th, 2014) and posted on the FDA website associated with the docket of the previous citizen petition within the briefing document and/or the presented powerpoint slide-show for this Type C meeting (see exhibit 6). These analyses reveal significant differences between the purported generics and Copaxone®.

In particular, the findings for Probioglat discussed below should be carefully addressed given the serious clinical reports from Mexico following introduction of this purported generic to the market. The complaints expressed by MS patients treated with Probioglat in Mexico included adverse reactions (increased injection site reactions and post injection reactions) and increased occurrence of relapses, even in patients who had been stable for years under Copaxone® treatment. These effects may be underlined by a biological imbalance between anti-inflammatory and pro-inflammatory processes, which may be discernible in gene expression differences such as those described below. The pro-inflammatory signal identified in pre-clinical analyses and its potential association with boosting of the autoimmune mechanisms of disease following switching to Probioglat treatment should raise concerns for the potential health consequences of these differences.

Teva's physicochemical testing on all putative generic products marketed to date reveals important differences as well. The purported generic products show some similarities to Copaxone® using low resolution physicochemical methods, but higher resolution physicochemical methods, as well as gene expression studies, have identified significant differences. The clinical implications of such differences are not fully characterized and may potentially be fully elucidated through standard prospective clinical trials. The Natco product (Glatimer®) exhibits considerable variations in key molecular weight parameters both among its *own batches* and as *compared to Copaxone®*, especially when applying tests that are designed to evaluate complex mixtures and polypeptide/protein structures. Thus, the Dynamic Light Scattering (DLS) measurements sensitive to *particle size* in the nano range detected significant deviation of Natco batches in comparison with Copaxone®; *charge distribution* driven by the primary structure of the polypeptide sequences was shown to be different between Copaxone® and Natco, as well as other purported generics, when analyzed using *capillary electrophoresis focusing*; differences in size and charge resulting in profoundly different morphological dimensions of the nano-sized colloidal particles suspended in the solution was revealed by *Atomic Force Microscopy;* and, finally, Natco and other purported generics were demonstrated to be compositionally different from Copaxone® when tested by *ion mobility mass spectrometry (IMSS),* a two dimensional technique that separates peptides based on size and mass/charge. The

analysis of the Natco product revealed that it had peptide compositions that vary significantly from Copaxone®, due to a combination of differences in amino acid sequence, length, and amounts of peptides in the product. Finally, a high degree of batch-to-batch variability was noted for the Natco product suggesting a lack of control in the manufacturing process.

Taken together, these tests raise serious concerns about the safety and efficacy, particularly in the long-term, of purported generic versions of Copaxone® currently being marketed overseas. These are especially relevant to the United States because Natco has partnered with one of the applicants for a generic version of Copaxone® in the US. Whether or not the identical API is intended for use in different markets, the issues identified in the Natco product raise concerns about the company's standard operating procedures and manufacturing control.

3. Clinical Implications of the Use of Purported Generics: Probioglat in Mexico – A Case Study

The above described differences between purported generics and Copaxone® could be the reason behind the clinical experience overseas where several reports of patients experiencing serious adverse reactions have been issued. Some of the most concerning reports come from Mexico, where Probioglat was first introduced in January 2013. The Patient Support Program that Teva operates to assist Copaxone® patients who reside in Mexico has received dozens of complaints from patients who have received Probioglat treatment—including reports detailing breakthrough relapses within mere weeks or months of exposure to Probioglat (even in patients who had been stable for years while treated with Copaxone®), and symptoms that include severe pain, burning sensation, fever, weakness, exhaustion, nausea, dizziness, loss of balance, mood changes, incontinence, shaking, swelling, vomiting, itching, rashes, numbness, and tremors. Many of those conditions required hospitalization. Public reports confirm what patients have described to Teva's Patient Support Program. In a media interview, a patient representing approximately 180 patients receiving treatment with Probioglat at the Mexican Social Security Institute recently reported:

> [Probioglat] does not have the same experience as the original [Copaxone®] or the same results and has caused us a lot of harm…. [There have been] many types of relapses. The simplest are like my case, [involving the use of] a cane, but there were [also cases of use of] a cane with four feet, wheelchairs, hospitalizations, temporary decrease and almost complete loss of vision, hearing, not being able to walk, chronic fatigue, and depression, which affects us very much.[17]

In another post, Alonso Muller (Agentina) further notes that after receiving these and other official reports from patients and healthcare providers, the Mexican government reportedly is

[17] Posted by Alonso Muller (Argentina), *IMSS Gives A Generic Drug That Affects Multiple Sclerosis Patients* (translated), Televisa Aguascalientes (Dec. 11, 2013), *at* http://www.televisaregional.com/aguascalientes/noticias/IMSS-da-medicamento-generico-que-afecta-a-pacientes-con-esclerosis-235464281.html (last visited May 7, 2014).

investigating—though that investigation does not reverse the complications that patients have already experienced in treatment with Probioglat.[18]

On February 5, 2014, Dr. Augusto Grinspan, Global Medical Director at Teva Pharmaceuticals and Dr. Juan Daniel Verdi, Mexico Medical Director at Teva Pharmaceuticals, visited Hospital La Raza in Mexico City, one of the major IMSS (Instituto Mexicano de Seguro Social) hospitals, to interview experienced physicians and obtain a better understanding of the reports published in local media. Dr. Grinspan and Dr. Verdi met Dr. Enrique Molina, head of the multiple sclerosis unit, and Dr. Humberto Juarez, head of the neurology department.

They were informed that the MS unit follows 983 patients: 232 patients are being followed regularly at the unit, while the rest are being followed in a more sporadic way as they are referred from peripheral clinics. 65 patients were at that moment under glatiramer acetate treatment.

At Hospital La Raza, healthcare providers ("HCPs") cannot write a prescription with the brand name, but rather only using an internal code. The pharmacy will deliver what treatment brand they have in stock at that moment. For the glatiramer acetate internal code, the pharmacy could deliver Copaxone®, or Probioglat, or sometimes the patient will receive both treatments. All patients under glatiramer acetate treatment at Hospital La Raza have been treated at some point with Probioglat.

Dr. Molina and Dr. Juarez have observed that once patients are switched to Probioglat, they present and complain of an increase in injection site reactions, particularly local reactions with pain and erythema as well as diffuse reactions of flush, pruritus and precordialgia. Almost every single patient has presented tolerability issues. Regarding efficacy issues, they mentioned that more than 50% of patients have presented, within the 2nd and 4th month after switch, a relapse. They have shared the case of a young woman who was stable under Copaxone® treatment for years, whereas a few months after switching she presented a severe relapse with multiple MRI lesions. Dr. Grinspan and Dr. Verdi had the opportunity to see the MRI in which multiple and diffuse lesions were present. Pictures illustrating injection site reactions (areas of approximately 10 cm diameter of erythema surrounding the injection site) have also been shared.

At Hospital La Raza, an average of 66 relapse-related hospitalizations is recorded each year. However, in 2013 (in which Probioglat was in use since January) this number jumped to as many as 187 hospitalizations. As this increase does not correlate with the increase in number of MS patients being followed at the hospital, the physicians attribute the relapse related hospitalization increase to the cases that were switched from Copaxone® to Probioglat. To avoid further relapses due to Probioglat, the physicians chose to switch patients out of glatiramer acetate altogether, thus avoiding further exposure to Probioglat.

[18] Posted by Alonso Muller (Argentina), *Cases Of Patients Affected By Generic Drugs Will Be Analyzed* (translated), Televisa Aguascalientes (December 13, 2013), *at* http://www.televisaregional.com/aguascalientes/noticias/Analizaran-casos-en-particular-de-afectaciones-por-medicamentos-genericos--236616131.html (last visited May 7, 2014).

Dr. Juarez and Dr. Molina have expressed that any time they have a case of relapse or a patient reporting any adverse event, they generate a report addressed to the IMSS office and from there the report goes to COCTI (Coordination of Technical Control of Supplies). The COCTI then should send this report to the COFEPRIS (Federal Commission for the Protection against Sanitary Risk, a regulatory body supervised by the Mexican Secretariat of Health). Dr. Juarez and Dr. Molina shared with Teva that they know that these cases exist in any patient switched to Probioglat regardless of the treating hospital, but the physicians believe that they remain one of the only HCPs (and one of the only hospitals) reporting to COCTI, and this situation worries Drs. Juarez and Molina.

COCTI usually conducts analyses in follow up to such reports. Indeed, a letter from COCTI dated February 3rd, informed physicians that a Probioglat lot was being withdrawn due to presence of foreign particles. Probioglat was reintroduced into medical practice as of mid May, 2014, and thus back in use by hospital La Raza patients. To this end, Copaxone® alone was used between February and mid May, 2014, however both Probioglat and Copaxone® were in use January, prior to Probioglat's withdrawal, and then again during the months May and June of 2014. A similar occurrence was reported in August 2013.

On February 6th Dr. Grinspan and Dr. Verdi of Teva Pharmaceuticals had a meeting with Dr. Badillo from Clinica 1 in Aguascalientes, in North-Central Mexico. Clinica 1 is an IMSS institution that treats some of the patients featured in the media complaining about Probioglat adverse events.

Dr. Badillo is the senior neurologist (within a group of three) who follows approximately 200 MS patients from Aguascalientes and the referral surrounding area. Dr. Badillo reported that immediately after switching to Probioglat his patients experienced pain at the injection site, as well as high incidence of big areas of erythema. Over time they developed subcutaneous fibrosis, clearly palpable nodular indurations. Regarding efficacy, Dr. Badillo also reports a high incidence of relapses occurring early after switching to Probioglat. He particularly mentioned a 46 year old female patient who had been stable for 9 years with Copaxone® treatment but, within mere 2 months upon switching to Probioglat had a severe relapse with quadriplegia from which the patient has only partially recovered. Dr. Badilllo submitted safety reports accordingly. The reporting process at this hospital is the same as the one described at La Raza above. In brief, the report is being sent to the IMSS office and from there it is sent to COCTI (Coordination of Technical Control of Supplies). COCTI then should send this report to the COFEPRIS (the Federal Commission for the Protection against Sanitary Risk, a regulatory body supervised by the Mexican Secretariat of Health). Patients suffering adverse events and relapses also complained together as a group directly to the IMSS central office.

The Teva Patient Support Program in Mexico has an extensive database. Given that patients can switch between branded and purported generic GA, all patients are kept within the database and are provided with patient support services. Interestingly, the database shows differences in patient reports between 2012, when patients in the program were receiving only Copaxone®, versus 2013, when patients were receiving both Copaxone® and Probioglat (Table 1). **These differences are highly statistically significant and indicate a non-random increase in the number of total adverse events reported, as well as in the subset of total number of**

reported relapses during the course of 2013 as compared with 2012 ($p < 2.2e-29$ and $p < 3e-11$ for adverse events and for relapses, respectively).

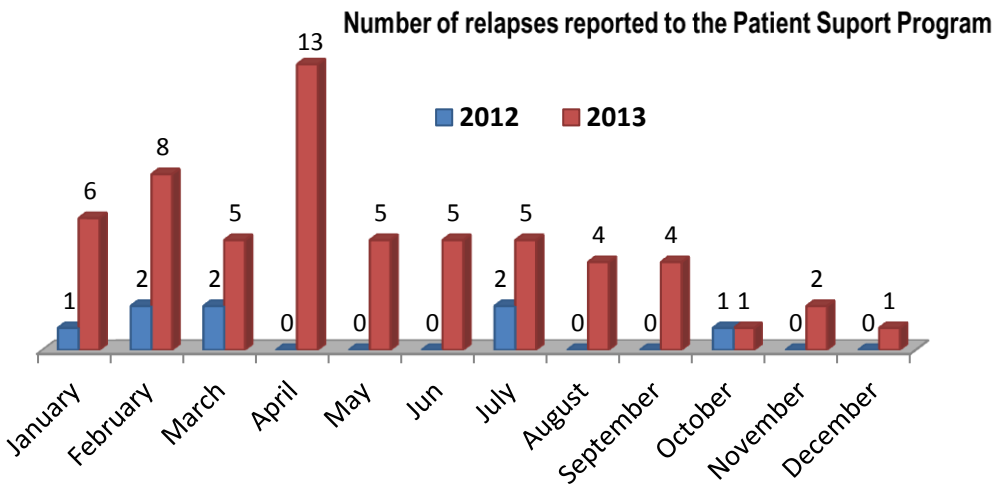
Table 1. Reported Adverse Events and Relapses in Teva's Patient Support Program, 2012-2013

	2012 (Copaxone® alone)	2013 (Probioglat+Copaxone®)	Statistical Significance of Increase from 2012 to 2013
Adverse Events	125	380	$p < 2.2e-29$*
Adverse Event Rate (per month)	10.4	31.7	
Relapses	8	59	$p < 3e-11$*
Relapse Rate (per month)	0.7	4.9	
Total Number of Patients in Teva's Patient Support Program	1618	1552	

* Single tailed p-value by Fisher's Exact test comparing the number of adverse events and relapses in 2012 < 2013.

Figure 1 depicts the number of relapses reported by patients in Teva's Patient Support Program on a monthly basis during the years 2012 and 2013. It is again clear that when Copaxone® alone was in use (i.e. throughout 2012) the overall, as well as per-month number of relapses was lower than that reported when Probioglat was present in the market (i.e. throughout 2013).

Figure 1. Relapses reported by patients in Teva's Patient Support Program



Patients have sent to the Patient Support Program pictures of the injection site reactions under Probioglat, reactions that they never had to such extent with Copaxone® (**Figure 2**).

Figure 2. Photos of the injection site reactions under Probioglat use posted by patients to the Patient Support Program



Teva forwarded the concerning findings described above to Probiomed (manufacturer of Probioglat). Additionally, on March 13, 2014, Teva sent a summary of the latest adverse events reported to the Patient Support Program to Dr María del Carmen Becerril, head of Pharmacovigilance at the Ministry of Health (COFEPRIS, Appendix 2). Teva representatives met Dr. Becerril to review the clinical reports, as well as the extensive gene expression data summarized herein on May 26, 2014. In parallel, patients themselves have expressed their

despair, sending letters to the IMSS and to their direct HCPs (copies of these letters were also shared with Teva and are enclosed in Appendix l).

In conclusion, Probioglat, a purported generic of Copaxone®, has been in commercial use in Mexico since January 2013. The introduction of Probioglat has resulted in a spike of injection site reactions and post injection reactions, as well as occurrence of relapses, even in patients who had been stably in remission for years. Accordingly, several pharmacovigilance reports have been issued by HCPs, and patients expressed complaints in the local media and in Teva's Patient Support Program.

The high occurrence of relapses and adverse events after the treatment switch to Probioglat may be due to an immunological imbalance favoring pro-inflammatory effects, instead of the well recorded beneficial effect that Copaxone® induces, reducing pro-inflammation and boosting anti-inflammation.

Overall, similarities in the physicochemical properties of the glatiramer acetate mixture are observed between Copaxone® and Probioglat, as well as other purported generics, particularly when using common non-specific analytical methods. However, clear differences are observed between Copaxone® and purported generics when applying high resolution methodologies targeted at characterizing functionally relevant elements, e.g. IMMS analyses concomitantly capturing composition, size and charge distribution; and gene expression analyses capturing pro-inflammation distinctly upregulated by purported generics but not Copaxone®.

Gene expression studies thus help explain the biological impact of the physicochemical differences observed, providing insight into some of the factors that may underlie the observed reduction in efficacy and parallel increase in adverse events reported with purported generic glatiramer acetate, notably Probioglat in Mexico. To this end, the next section details the analyses conducted to elucidate the genomic signatures induced by purported generics as compared with Copaxone®, and specifically with Probioglat in the section below discussing gene expression studies in human monocytes.

B. New Gene Expression Studies Suggest That Proposed Generic Glatiramer Acetate Products May Have Structural and Compositional Differences From Copaxone® That Affect Safety and Efficacy

As part of its ongoing commitment to better characterize Copaxone®, Teva has conducted high throughput gene expression analysis studies. As discussed in Teva's prior Petition (Exhibit 2), these studies raise significant concerns that proposed generic glatiramer acetate products manufactured via a different process and using a different starting material could have undetectable structural and compositional differences from Copaxone® that compromise the safety and/or effectiveness of the product. These tests thus underscore the importance of applying rigorous standards with respect to active ingredient sameness, immunogenicity and bioequivalence testing before FDA approves any purported generic versions of Copaxone®. A more thorough discussion of the methods used and results obtained from these studies, which is intended to address FDA's request for additional information, is provided below.

1. Overview of Gene Expression Analyses

a. Methodology for Gene Expression Analyses

The core analysis methods used for these studies are highly standard in the field (experimental design methodologies: Churchill, Nat. Genet., 2002; microarray data normalization method: Quackenbush, Nat. Genet., 2002; batch correction methodology: Johnson et al, Biostat, 2007; differential expression methodology: Smyth, Stat Appl Genet Mol Biol., 2004). New approaches were developed for particular questions where noted below (e.g., methods to determine enrichment for immunological cell types); all new analysis methods applied in the discussion below were evaluated and published via peer review.

The null hypothesis in traditional gene-expression studies, including Teva's studies with the glatiramoids, is that no significant gene expression differences are induced between the treatments. As such, the expectation is that regardless of the biological system used for testing, genes must show no statistically significant nor biologically meaningful differences among the different treatments. Only in cases where the treatments induce significant observable effects will probesets for genes differentially expressed between treatments pass the stringent statistical tests, and false discovery rate (FDR) correction for multiple hypotheses [Benjamini Y, Hochberg Y (1995) Controlling the false discovery rate: a practical and powerful approach to multiple testing. Journal of the Royal Statistical Society Series B (Methodological): 289–300]. These stringent requirements were imposed a priori across all tests to ensure robustness of results and minimizing of spurious results (i.e. risk missing true associations as a trade off to reduction in false negative results). Such statistically significant differences, if biologically meaningful (e.g., related to the disease biology or any of the drug's known or putative targets and downstream pathways), warrant further studies, as two drugs that have identical activities in biological systems should not induce statistically observable and biologically enriched differences when compared against each other.

b. Rationale for Gene Expression Analyses

Since traditional biological characterization methods (e.g. ELISA, secreted cytokine screens) are insufficient to fully characterize Copaxone®'s complex mode of action (or any other glatiramoid's), Teva pursued genome-wide unbiased analysis of expression arrays (>45,000 mRNA probesets, without choosing which genes to focus on or study). Comparative analysis was conducted to characterize the expression profile following stimulation by a variety of glatiramoids, including marketed products worldwide. The unbiased approach allowed identification of genes and pathways with subtle, yet robust, differential expression patterns following stimulation by the different glatiramoids in different experimental contexts. The functionality of identified genes and pathways was then described based on the peer-reviewed literature. Teva sought to characterize biological effects and qualitatively describe phenomena of similarity and differentiation. None of the studies were aimed to develop an analytical biomarker of similarity. The goal was to apply robust methods (high number of replicates, conditions and time-points, where relevant) in order to describe pathways changed by different treatments out of the entire milieu of genomic patterns. Further, additional hypothesis free methods indicated enrichment patterns that powerfully distinguish systematic patterns from random noise or functionally non-relevant effects.

In summary, these studies were not designed to establish a particular set of analytical tests by which sets of genes will be defined as a panel to evaluate sameness between Copaxone® and differently manufactured glatiramoids. Rather, the fact that statistically significant differences were observed between Copaxone® and differently manufactured glatiramer acetate preparations, and the fact that these differences were in genes highly relevant to disease processes and drug response mechanisms, indicate a need to investigate drug equivalence further in systems meaningful for safety and efficacy profiling (specifically, pre-clinical immunologically relevant systems such as those described below, complemented by a standard clinical trial with appropriate sufficient follow-up period).

The next few sections describe two types of studies in which gene expression analysis was used to address various scientific questions about Copaxone® and its purported generics.

2. Gene Expression Studies in Mouse Splenocytes

a. Batch-to-Batch Variability Observed with Natco Product

Initial gene expression studies were conducted in mice and designed to model the biological impact of a switch from Copaxone® to generic. A complete discussion of the mouse splenocyte gene expression results summarized here can be found in the Type C Meeting FDA Briefing Package document, and in two peer-reviewed publications: Bakshi, S. et al. Gene expression analysis reveals functional pathways of glatiramer acetate activation. Expert Opinion on Therapeutic Targets 17, 351–362 (2013) (Exhibit 12), and Towfic et al., Comparing the biological impact of Glatiramer Acetate with the biological impact of a generic, PLOS One (2014) (Exhibit 5).

Among other findings, Teva's gene expression analysis of the purported generics revealed batch-to-batch inconsistency within purported generic versions, including Natco Pharma Ltd.'s ("Natco") Glatimer® which currently is marketed in India and Ukraine. The initial analysis revealed that using standard clustering methods, the gene expression results of the purported generic naturally clustered into two different groups: one including three samples from two different manufacturing batches, and the second including eight samples from three different manufacturing batches. This analysis strongly suggests heterogeneity in the manufacturing process of the purported generic, and was described in a peer reviewed publication.[19]

Teva then employed an advanced analysis of gene expression from all five batches of the purported generic and 30 batches of Copaxone®. That analysis revealed that the purported generic had a variable impact on four times as many genes as Copaxone®, which by contrast is highly consistent from batch-to-batch. A peer-reviewed published analysis suggests that these differences may be due to variability in the products' manufacturing processes, and that the

[19] Bakshi, S. et al. Gene expression analysis reveals functional pathways of glatiramer acetate activation. Expert Opinion on Therapeutic Targets 17, 351–362 (2013) (Exhibit 12).

specific subset of genes most impacted by this variability include genes highly relevant to Copaxone®'s mechanism of action as further discussed below.[20]

b. Genes significantly differentially modulated by Copaxone® versus Natco are enriched in highly relevant immunological cell types

The initial gene expression studies [Bakshi et al] also revealed that Copaxone® modulated expression levels of 98 genes differently when compared to purported generic versions (after a 1.3 fold change cutoff), and subsequent analyses found over 700 genes to be differentially expressed (without a 1.3 fold change cutoff).[21] Unsurprisingly, each treatment produced many overlapping gene expression changes, but importantly, the subset of genes differentially expressed between treatments was not a random group of genes but rather a highly significant group of immunologically relevant genes, including those characteristically and specifically expressed in a set of immune cell types involved in the pathoetiology of MS (e.g., regulatory T cells and monocytes).[22] See Figure 3, illustrating the different cell types modulated in the comparison between the two drugs (Towfic et al, Fig. 3). FOXP3+ T cells are upregulated by Copaxone® relative to Natco; macrophages and monocytes are upregulated by Natco relative to Copaxone®. The upregulation of monocyte markers is also illustrated in Figure 4.

[20] Towfic et al., Comparing the biological impact of Glatiramer Acetate with the biological impact of a generic, PLOS One (2014) (Exhibit 5).

[21] Towfic et al, Table S5 (attached hereto as Supplementary Table 1).

[22] Towfic et al, Table S8 (attached hereto as Supplementary Table 2).

Figure 3. Cell-type specific differences in the biological impact of GA and generic. The heat map depicts relative expression of specific genes in GA-activated samples and generic activated samples. Each of the rows within the Treg section represents a gene with a high cell-type specificity scores for Tregs, while each of the rows in the macrophages and monocyte sections represents genes with high cell-type specificity scores for each of those cell types. The associated gene lists appear as supplementary information. Overall, GA induces higher expression of Treg-associated genes than generic, while generic induces higher expression of macrophage and monocyte-associated genes than GA. [Figure and legend reproduced from Towfic et al; GA=Copaxone®; "generic"= Natco.]

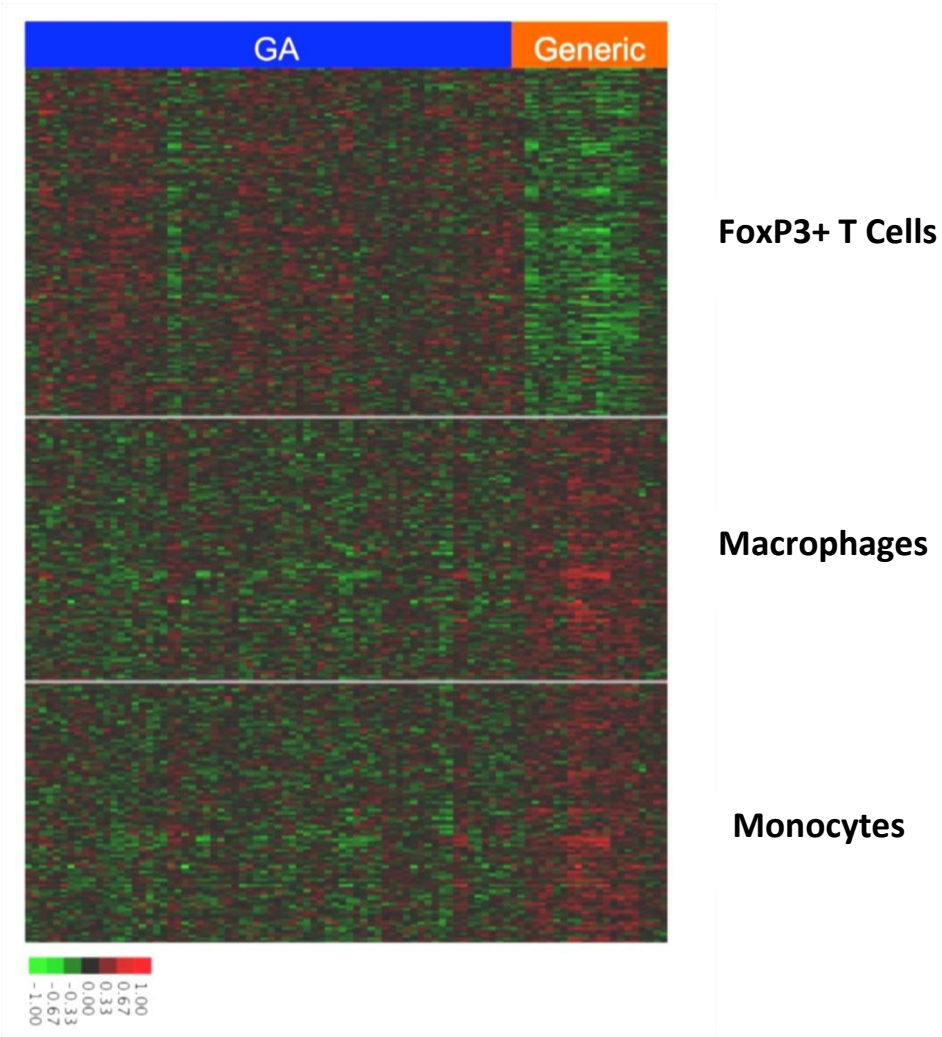
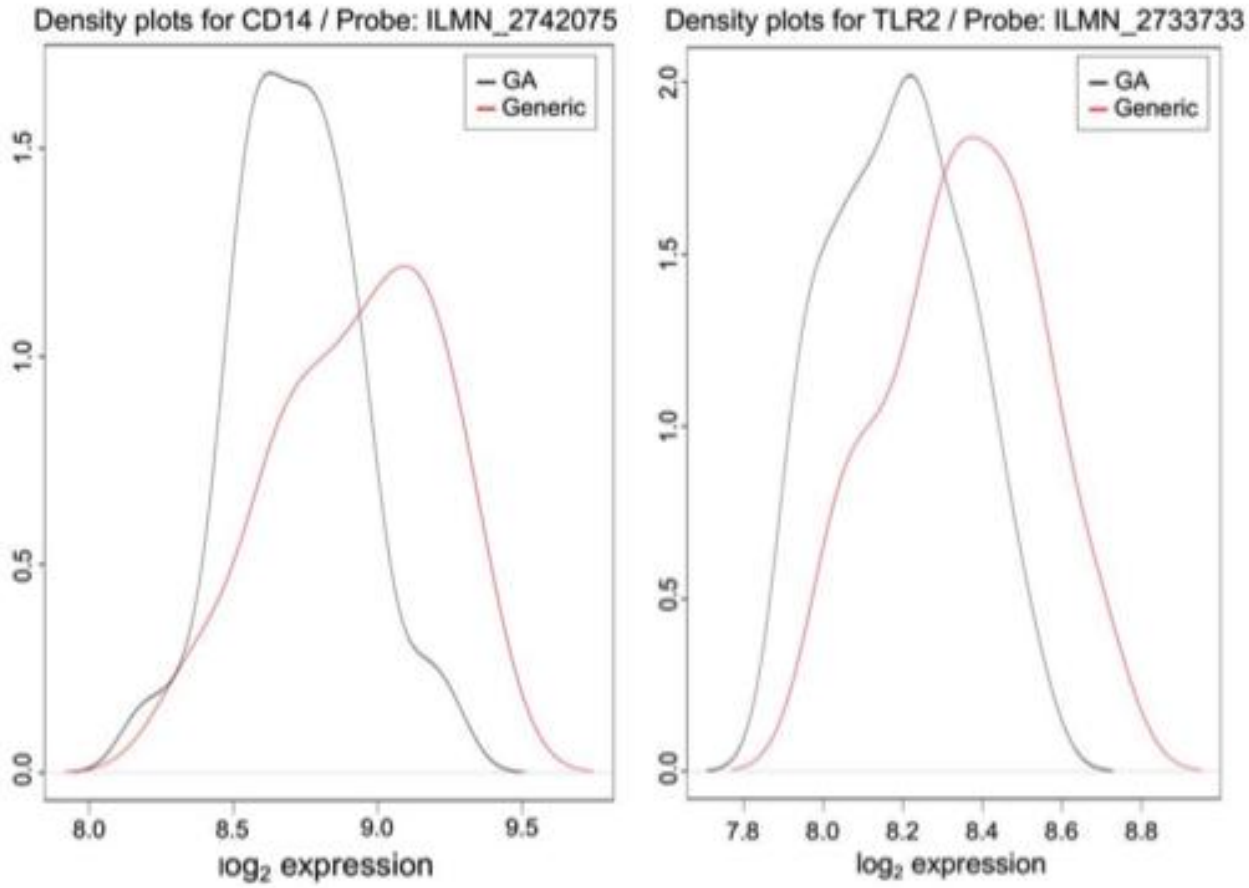


Figure 4. The generic's impact on monocytes may differ from GA's impact. Generic induces significantly higher expression of CD14 and TLR2, as determined by a Wilcoxon rank sum test and depicted as kernel density plots, which can be likened to a smoothed histogram. [Figure and legend reproduced from Towfic et al Figure 4 part A; GA=Copaxone®; "generic"=Natco.]

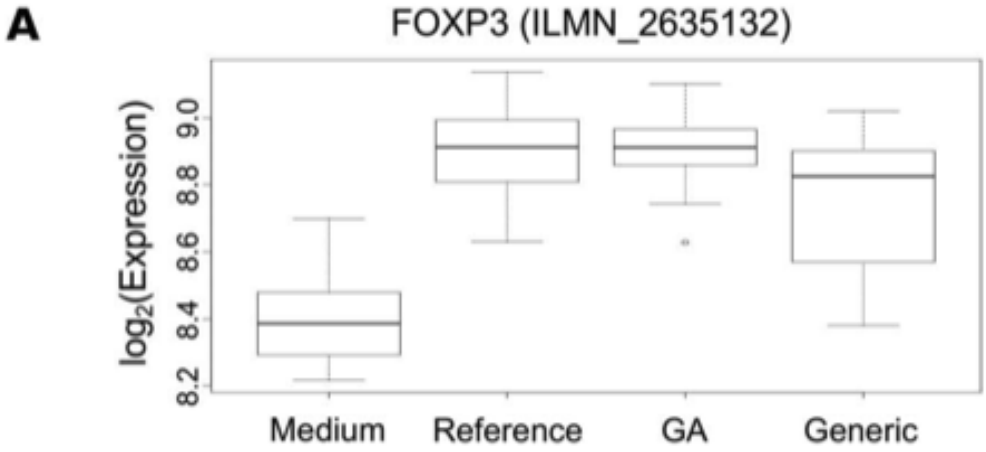


T-regs are immunomodulatory cells that are known to suppress myelin reactive T-cells and contribute to positive response in MS patients (Wang et al, Journal of Clinical Investigation, 2006) while monocytes have been shown to be associated with disease severity and duration (Kouwenhoven et al, J Neuroimmunology, 2001). The expression pattern of these genes and pathways in particular should not differ between treatments that purport to have similar mechanisms of action and are intended for use in patients suffering from an autoimmune disease. These differences strongly indicate a need to further study and evaluate the health consequences in a clinical context, in order to protect patients from potential consequences of switching therapies.

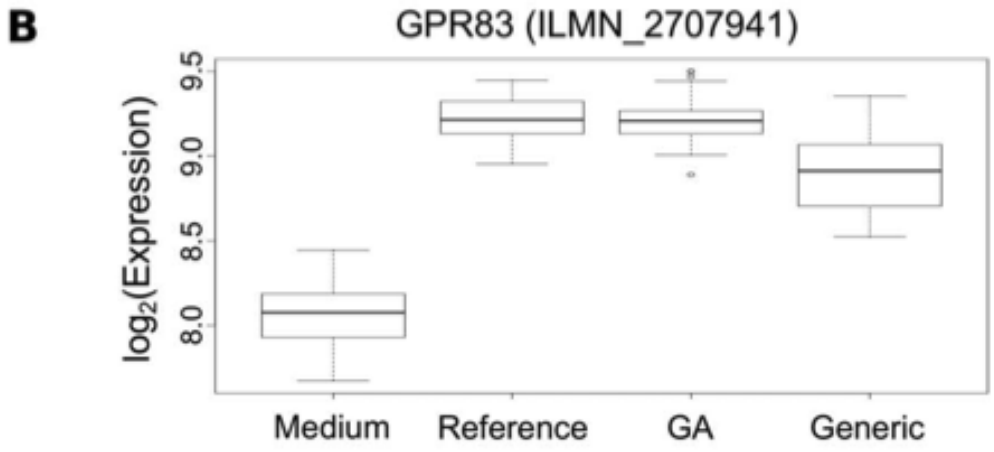
c. Genes significantly differentially modulated by Copaxone® versus Natco include crucial immunological markers relevant to GA mechanism of action

To understand the biological impact of the observed variability in Natco, **all** 45,000+ probesets on the chip were ranked by the ratio of their variance in Natco to variance in Copaxone®. In this analysis, the #1 ranked probeset was for FOXP3 (F test p value 8.28e-06) and the #2 ranked probeset was for GPR83 (F test p value 9.17e-06) [Towfic et al], meaning that these two genes were the most impacted by Natco's variability. See Figure 5, reproduced from Towfic et al (Towfic et al Figure 2), showing expression levels of FOXP3 and GPR83. Such results are striking because FOXP3 and GPR83 are critically important genes: both are established biomarkers for tolerance-inducing regulatory T cells ("Tregs"), which play an important role in preventing autoimmune damage—particularly in the context of MS, where patients' cells express significantly reduced *FOXP3* levels. *FOXP3* (forkhead box P3) is the key transcription factor controlling Treg development and function, and as such is considered to be the "master-regulator" for the Treg lineage. Induction of the FOXP3 gene in normal naïve T cells converts them to Treg-like cells with in vivo and in vitro suppressive function, indicating that FOXP3 is likely to play a key role in controlling expression of critical suppression-mediating molecules. *GPR83* is one of FOXP3's targets, and has been reported as a specific and stable cell surface marker with modulatory properties, key for characterization of the molecular basis of Tregs.

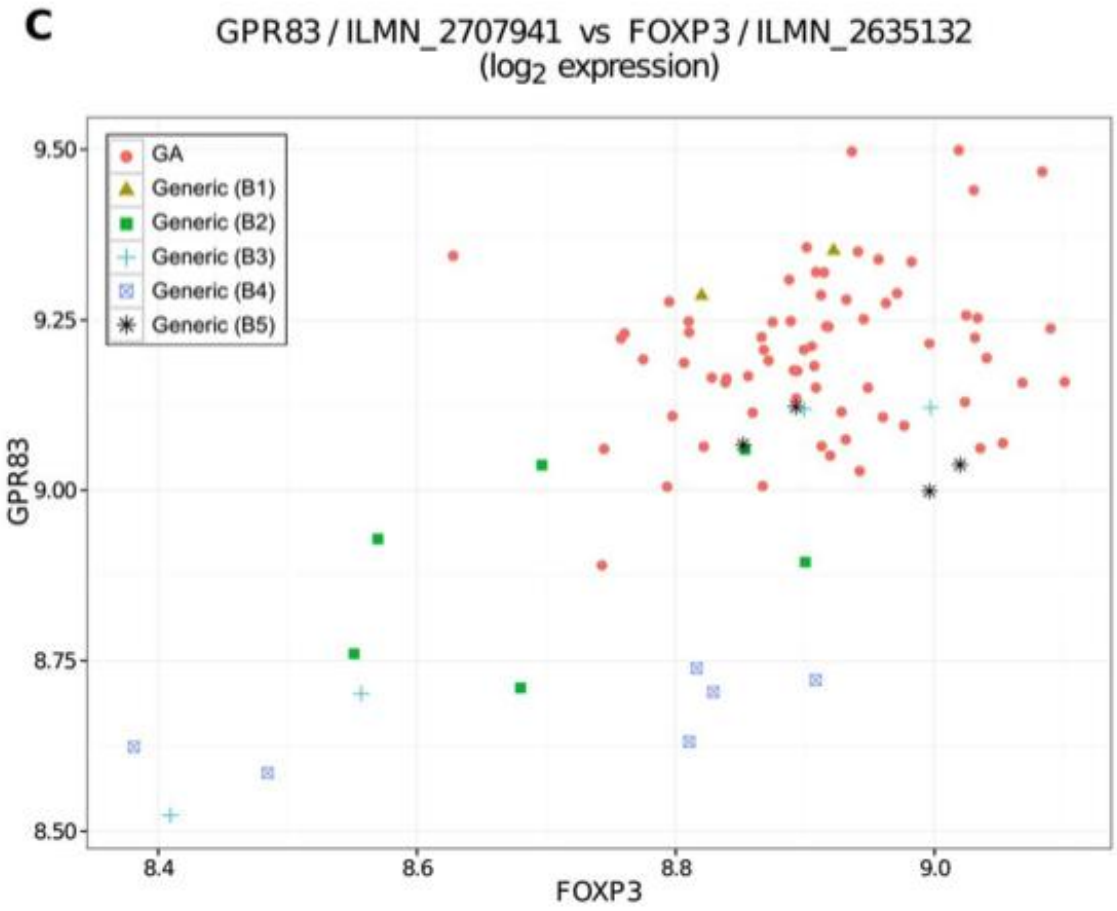
Figure 5. Copaxone® induces Tregs more effectively than the purported generic, Natco. (A) Copaxone® (GA) induces significantly higher expression of the key Treg marker FoxP3, compared with the purported generic, Natco. [Figure parts A-C reproduced from Towfic et al, Figure 2; Part D reproduced from FDA Type C Meeting Slides (Exhibit 6)]



(B) Another key Treg marker, Gpr83, shows a similar pattern of expression, with Copaxone® (GA) inducing a significantly higher expression level compared with Natco ("generic").

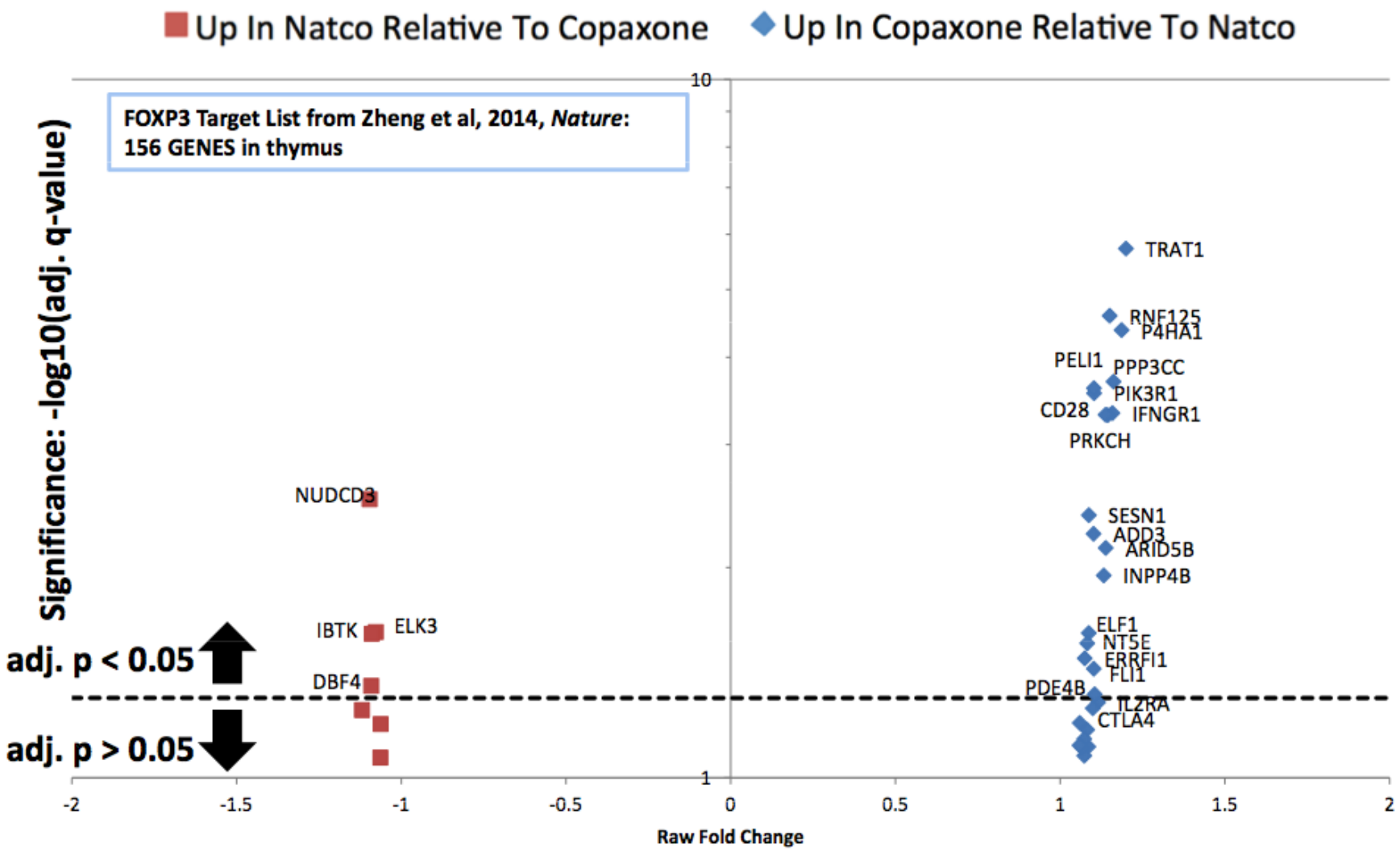


(C) Both FoxP3 and Gpr83 are low in the same samples as indicated by scatter plot, further strengthening the case that generic fails to induce a strong Treg response in some patients. B1-B5 refer to batches of Natco ("generic").



(D) As further evidence of the difference in FoxP3 induction, GSEA analysis found a significantly stronger upregulation of FoxP3 target genes in Copaxone®-activated samples than in generic-activated samples, as well as a significant enrichment of Treg-specific genes among the genes with higher expression in Copaxone® (GA) than in Natco ("generic").

D



Gene Set Enrichment Analysis (GSEA): Subramanian et al, 2005, *PNAS*, Results: Towfic et al, 2014, *PLOS ONE*

As an independent corroborating convergence method, analysis of downstream targets of FOXP3 previously reported in Nature (Zheng et al, Nature, 2007 doi:10.1038/nature05563) also found these targets to be highly enriched among the genes upregulated to a greater extent by Copaxone® than by Natco (Towfic et al, Table S6; attached here as Supplementary Table 3). Again, Copaxone® upregulates *FOXP3, GPR83* and their downstream induced pathways at a higher level and with greater consistency than the purported generics, raising serious concerns about the purported generic product's efficacy as a long term treatment for MS.

d. Discussion

The mouse splenocyte experiments indicated that the upregulation of the immunosuppressive T-reg specific markers (FOXP3 and GPR83) was more consistent in Copaxone®-treated compared to Natco-treated splenocytes. Another major result from that paper is that genes specific to pro-inflammatory monocytes and macrophages were upregulated to a greater extent by Natco compared to Copaxone®-treated splenocytes. Such results show that Copaxone® modulates multiple cell types and genes in this experimental setup. The diversity of cell types modulated by the drug makes it difficult to define a small set of genes to use as quality-control measures against a given Copaxone® lot. Using this splenocyte experiment, we note that over 9,000 probesets (over 5,000 genes) passed our strict FDR < 0.05 threshold for being differentially expressed due to Copaxone® treatment relative to control (medium). **As such, using genome-wide gene-expression arrays as part of well-powered experiments is necessary to fully characterize the similarities or differences between Copaxone® lots or generics due to the many genes modulated by Copaxone® even in this simple model system.**

e. Summary

The above sub-section summarizes the main results of the differences observed in the mouse splenocyte gene expression studies following treatment with Copaxone® versus Natco. As previously mentioned, these results are discussed in extensive detail in the Type C Meeting FDA Briefing Package document. The same briefing document also presented initial results from experiments conducted in human monocytes. Further analyses described in the slides from, and further analyzed since, the FDA Type C meeting are described in the next section. Teva continues to elucidate differences and similarities across glatiramoids and their clinical relevance.

3. Gene Expression Studies In Human Monocytes

In order to evaluate the human relevance of the initial findings in the mouse model, and to better allow linking to clinical utility, Teva conducted experiments in the human monocyte (THP-1) cell line comparing Copaxone® with other purported generics, including Probioglat (sold in Mexico). The choice of THP-1 cells as a model system was motivated by the modulation of monocyte-related genes in the mouse splenocyte study, and the fact that these cells are known to express HLA-DRB1*15 as well as other cellular features relevant to Copaxone® therapeutic effect.

The tests revealed that genes significantly upregulated by Probioglat relative to Copaxone® were enriched for inflammatory pathways and included key pro-inflammatory genes

that could be harmful to MS patients. At the same time, Probioglat downregulated several anti-inflammatory genes (which are likely beneficial for MS patients), compared to Copaxone®. Results were corroborated by gene-level, pathway-level and independent qRT-PCR analyses.

a. Results: Copaxone® Mechanism of Action

To gain insight into the mechanism of action of Copaxon®e, we examined the effect of Copaxone® treatment on THP-1 human monocyte cells. mRNA expression levels were compared between treatment with Copaxone® and control (mannitol) with 4 batches of Copaxone® and a total of 6 samples/replicates for mannitol and for each batch of Copaxone®, using LIMMA (Smyth et al, Stat Appl Genet Mol Biol 2004) (Methods). Many genes were modulated significantly (FDR adjusted p value < 0.05) at each timepoint by treatment with Copaxone® (Table 2; Supplementary Table 4 for listing of top modulated probesets). For example, at 6 hours of Copaxone® treatment, 2824 genes were significantly upregulated by FDR adjusted p value < 0.05 (3511 genes by nominal p value < 0.05) and 4066 genes were significantly downregulated by FDR adjusted p value < 0.05 (4909 genes by nominal p value < 0.05). Fewer genes were modulated significantly as the treatment time increased, with approximately half as many modulated at 12 hours, and approximately a quarter as many at 24 hours (Table 2). We chose 6 hours for initial downstream analysis, as the time point reflecting the greatest impact of treatment in this model system.

Table 2. Numbers of genes significantly modulated by Copaxone® treatment at each timepoint.

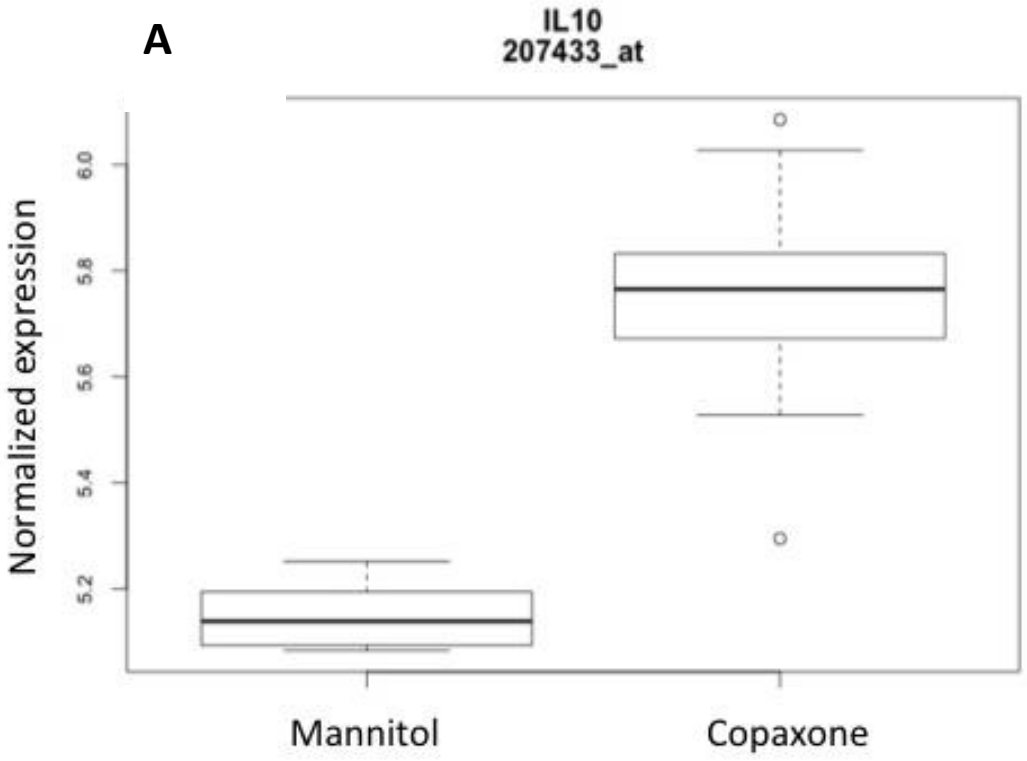
	6 hr		12 hr		24 hr	
	Upregulated	Downregulated	Upregulated	Downregulated	Upregulated	Downregulated
nominal p < 0.05	3511	4909	2377	3430	1410	3724
FDR p < 0.05	2824	4066	1308	1810	606	1185
FDR p < 1e-5, |FC|>=1.5	257	119	68	10	15	0
FDR p < 1e-5, |FC|>=1.3	557	508	210	50	57	6

* FC – Fold Change; FDR – False Discovery Rate correction

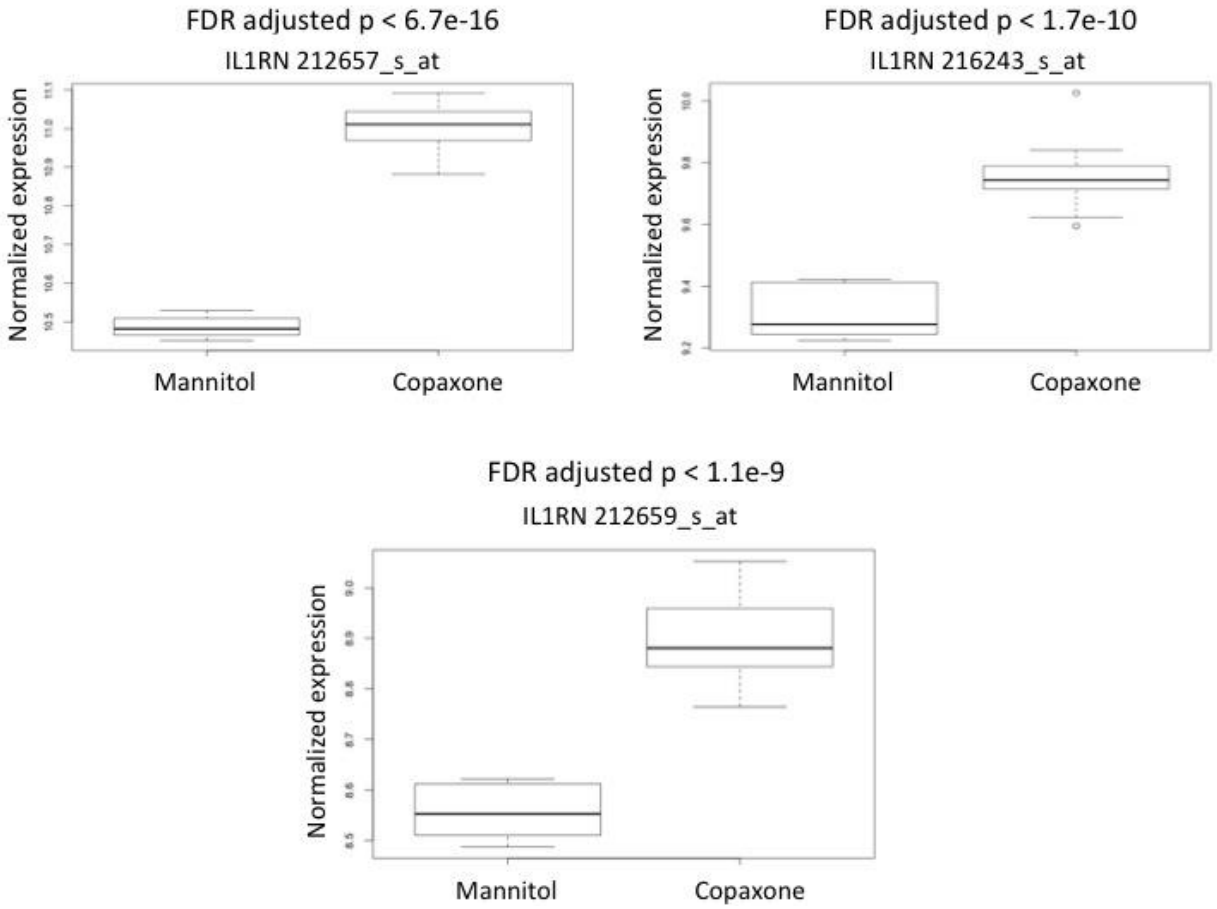
The fact that levels of Copaxone® persist in the cell culture medium out to 24 hours (Supplementary Figure 1) indicates that this observation is unlikely to reflect a decrease in concentration of drug. Rather, this decrease in number of genes affected from early to later timepoints represents an attribute of the response of the cells to the drug. That is, Copaxone® induces a larger effect on gene expression at 6 hours compared to the later timepoints (Table 2). The use of this early timepoint may indeed be most relevant given Copaxone® action in vivo, as intact Copaxone® is thought to be rapidly degraded at the site of injection, eventually without measurable blood levels (Comi et al, Neurol 2002, Rizvi et al, Int J Nanomed 2006).

The differentially expressed genes included several anti-inflammatory genes. IL10, the gene for the anti-inflammatory cytokine IL-10, was upregulated at the 6 hour timepoint (FDR adjusted p value 3.1e-9; Figure 6A). IL1RN, which codes for IL-1ra, a protein that inhibits the activities of IL-1a and IL-1b, was upregulated at all three timepoints (FDR adjusted p values 6.7e-16, 3.9e-11 and 0.001, at 6, 12 and 24 hours, respectively) (Figure 6B).

Figure 6. Increased expression of IL10 with Copaxone® treatment at 6 hours. (A) for the single IL10 probeset on the array (207433_at), FDR adjusted p < 3.1e-9)



(B) Increased expression of IL1RN following Copaxone® treatment at 6 hours for multiple probesets



To determine whether the differentially expressed genes related to one another in a coordinated fashion, top significantly upregulated and downregulated genes were examined for pathway enrichment using DAVID (Huang et al, Nucleic Acids Res 2009) as described in the Methods section below. Fold change and p value filters were used to obtain top gene lists of appropriate size (i.e. tens to hundreds) for use with DAVID.

The enriched pathways are illustrated in Figure 7 and listed in Supplementary Table 4. The top genes significantly upregulated by Copaxone® in the human THP-1 cell line at 6 hours of treatment were enriched significantly (by Benjamini corrected p value < 0.05) for 114 pathways (Supplementary Table 4), including many immune-related pathways. For example, the regulation of immune system process (GO:0002682) and cytokine-cytokine receptor interaction (hsa04060) pathways were both significantly enriched among the top upregulated genes. The top upregulated genes identified as members of the cytokine-cytokine receptor interaction pathway are shown in Figure 8. In addition, 9 pathways were significantly enriched among genes downregulated by Copaxone® (Supplementary Table 4).

Figure 7. Pathways enriched among top genes modulated by Copaxone® at 6 hours (restricted to fold-change and adjusted p value filters of 1.5 and 1e-5, respectively).

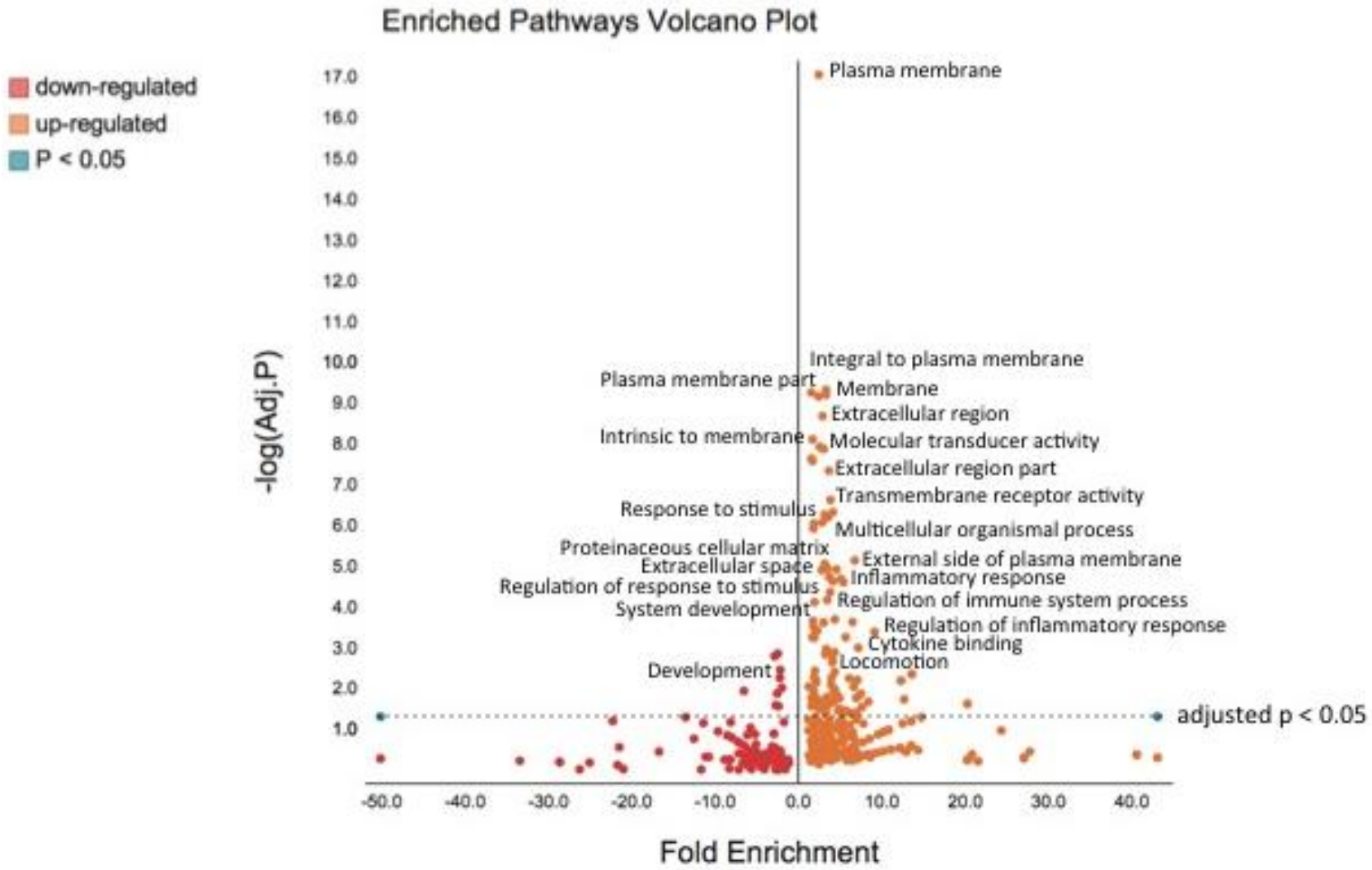
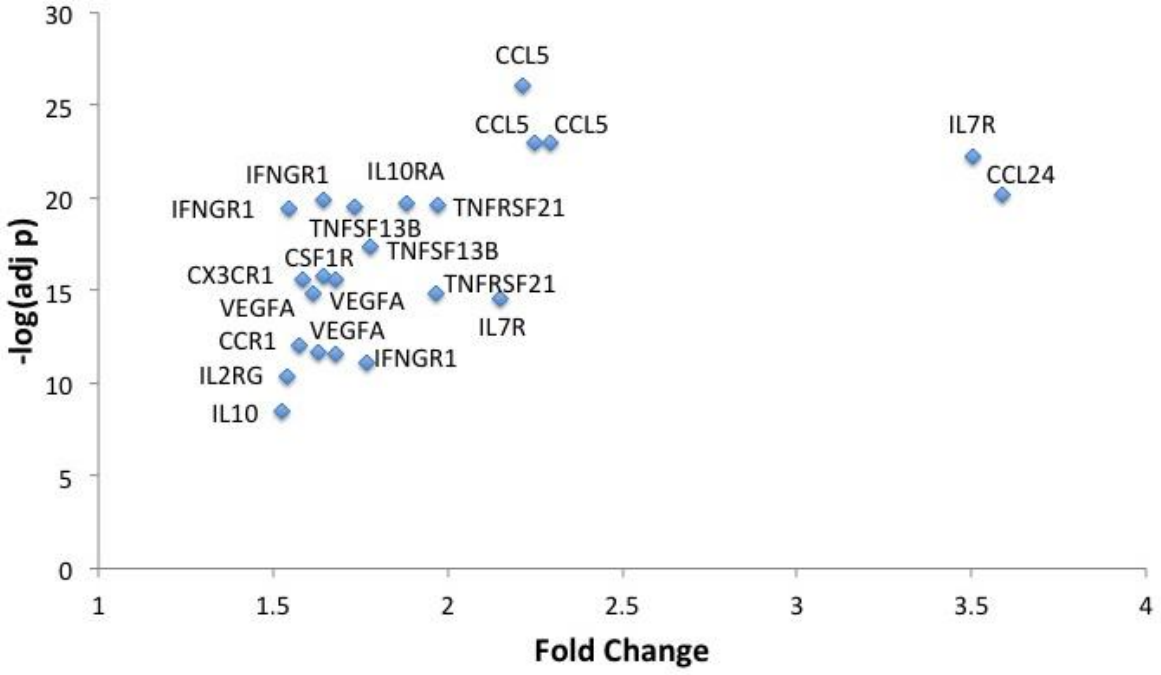


Figure 8. Probesets for cytokine-cytokine receptor interaction pathway genes significantly modulated by Copaxone® at 6 hours (restricted to fold-change and adjusted p value filters of 1.5 and 1e-5, respectively).



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b. Results: Differences in gene expression induced by Probioglat versus Copaxone®

To identify differences between Copaxone® and differently manufactured glatiramoids, we performed differential gene expression analysis to compare directly between profiles induced by Copaxone® and by the purported generic Probioglat. The standard R LIMMA bioconductor package was utilized to measure differentially expressed probesets across the entire microarray. Many significant differences were observed between Copaxone® and Probioglat. Table 3 lists the numbers of differentially expressed genes by stimulation time and statistical significance threshold. As expected based on the more extensive response to Copaxone® at 6 hours, the most differences were observed at the 6 hour timepoint (see Supplementary Table 6 for the full list of differentially expressed probesets at 6 h; 126 upregulated, 22 downregulated).

Table 3. Dynamic profiles of differentially expressed RNA after stimulation of THP-1 cells by Probioglat versus Copaxone®

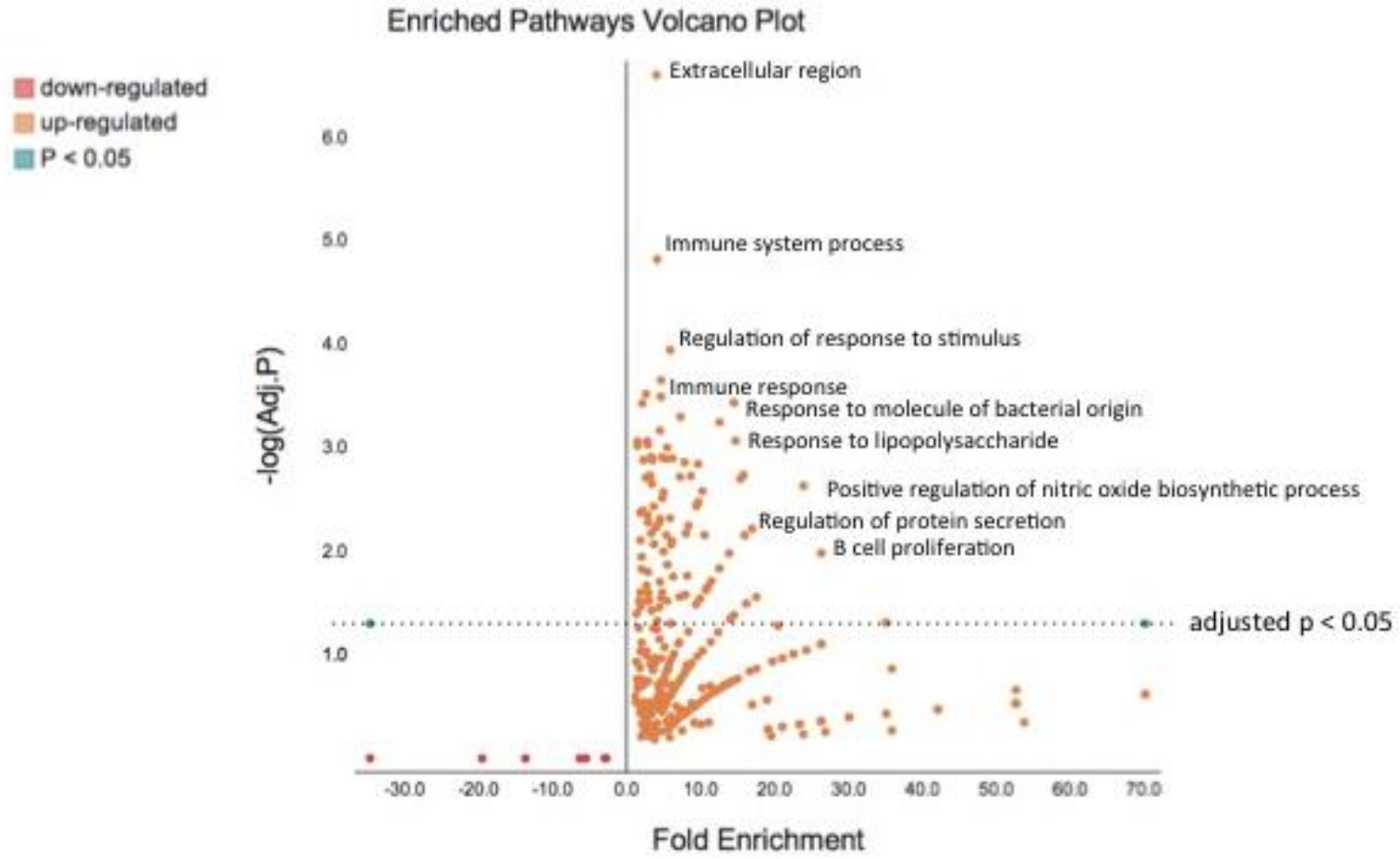
Stimulation time	6 hours			12 hours			24 hours		
	Genes	Probeset		Genes	Probeset		Gene	Probeset	
Significance threshold	#	#	% *	#	#	%*	#	#	%*
FDR adjusted p value < 0.05	115	138		5	5		1 (*MMP*9)	1	
Nominal p value < 0.05	4,668	6,028	13%	2,989	3,992	8%	2,774	3,486	7%

* represents percent of probesets detected as significantly differentiated between treatments as percentage of the total 47,000 probesets included in the Affymetrix U133 Plus 2.0 chip.

These differences included proinflammatory genes that were increased in expression by Probioglat relative to Copaxone®, including CCL5, CCL2, MMP9, MMP1, CXCL10, CD14, ICAM1 and BIRC3 (all significant by FDR adjusted p value < 0.05, as listed in Discussion). At the same time, differences were observed in levels of anti-inflammatory genes. Probioglat downregulated anti-inflammatory genes CISH and HSPD1 relative to Copaxone®, and upregulated IL10 and PRDM1 relative to Copaxone® (all significant by FDR adjusted p value < 0.05, as listed in Discussion).

We performed pathway enrichment analysis using DAVID on the genes significantly upregulated and downregulated by Probioglat relative to Copaxone®. No pathways were enriched significantly among downregulated genes. 106 pathways were enriched significantly (Benjamini corrected p value < 0.05) among genes upregulated by Probioglat relative to Copaxone®. The pathway enrichment results are illustrated in Figure 9, and the list of these pathways is provided in Supplementary Table 7. These pathways include immune system process (GO:0002376), response to lipopolysaccharide (GO:0032496; Figure 10) and many other immune system related pathways.

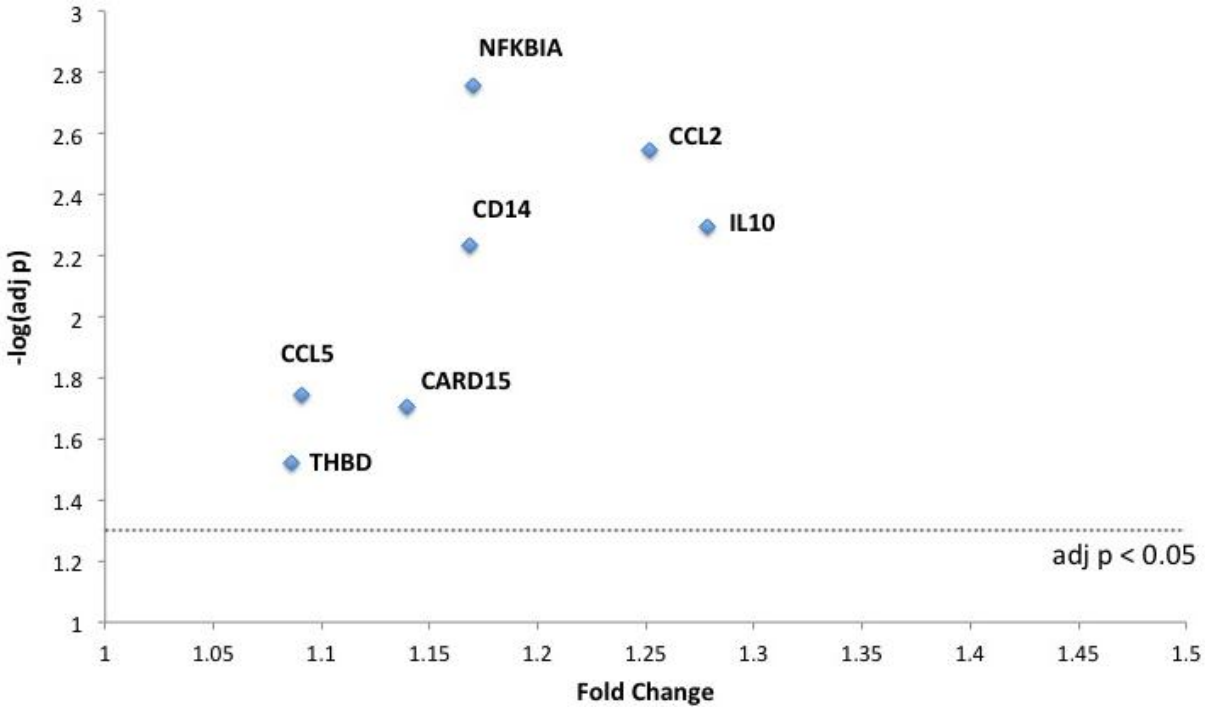
Figure 9. Pathway-level analysis depicts enrichment among genes upregulated by Probioglat stimulation compared with Copaxone® at 6 hours.



LPS – Lipopolysaccharide; NOD - nucleotide-binding oligomerization domain receptor

Supplementary Table 7 includes the full list of pathways identified and their associated p values.

Figure 10. Focus on the "response to LPS" pathway as differentially expressed by Probioglat versus Copaxone® at 6 hours.



c. <u>Validation of pro-inflammatory markers' upregulation by stimulation with Probioglat compared to Copaxone® (qRT-PCR analysis)</u>

In order to validate the results from the microarrays comparing Probioglat with Copaxone®, two chemokines (CCL5, FDR p-value < 0.02 and CXCL10, FDR p-value < 0.0006), two matrix metalloproteinases (MMP1, FDR p-value < 0.002 and MMP9, FDR p-value < 2.8e-6) and a cell surface marker (CD9, FDR p-value < 0.002) that is a component of myelin and a marker of myelinogenic progenitor cells [Sim et al, Nature Biotechnology, 2011] were tested independently by robust qRT-PCR analysis (see Methods for details). Three Copaxone® batches and one Probioglat batch were available for use, and **a total of 360 observations from each transcript were evaluated.** Statistical analysis utilized a one-sided t-test with unequal variance to compare the RNA expression from the two treatments. **All the genes tested were significantly differentially expressed between Probioglat and Copaxone® as expected based on the microarray analysis**. Table 4 shows p-values from single-tailed t-test with unequal variance (for qPCR results) and FDR-adjusted p-values from LIMMA comparison of microarray data between human monocytes treated with Copaxone® and Probioglat.

Table 4. Differential expression (p value and fold change) of key immunological genes following Probioglat stimulation compared with Copaxone®

Genes	CCL5		CD9		CXCL10		MMP1		MMP9	
Method	**FC**	**p value**	**FC**	**p value**	**FC**	**p value**	**FC**	**p value**	**FC**	**p value**
qPCR	1.12	4.05E-05	1.11	0.0004	2.28	0.0029	1.25	0.0201	1.24	0.0168
FDR-adjusted Microarray	1.09	0.02	1.15	0.002	1.46	0.0006	1.5	0.002	1.29	2.80E-06

d. Discussion

1. Gene expression changes induced by Copaxone® are consistent with its known mechanism in MS

The many significant gene expression changes observed in the human THP-1 cell line due to treatment with Copaxone® included changes consistent with previous literature (as discussed below), supporting the validity of the current study design for revealing relevant effects of treatment.

For example, expression of the anti-inflammatory gene IL10 was increased at the 6 hour timepoint, consistent with what is known about Copaxone® mechanism with regard to monocytes. As discussed above, Copaxone® is thought to induce an anti-inflammatory effect, mediated by secretion of IL-4, IL-10, and other anti inflammatory cytokines both in terms of T cells (Th1 to Th2 shift) but also in terms of monocytes, resulting in a shift from monocyte production of IL-12 to anti-inflammatory IL-10. For example, monocytes from mice treated with Copaxone® secreted more IL-10 than monocytes from untreated mice (Weber, Nat Med 2007), and monocytes isolated from MS patients treated with Copaxone® were shown to upregulate IL-10 relative to untreated patients (Kim, J Immunol 2004). In addition, dendritic cells exposed to Copaxone® during maturation increased their production of IL-10 (Vieira et al, J Immunol 2003).

Another anti-inflammatory gene, IL1RN (which codes for IL-1ra, a protein that inhibits the activities of IL-1a and IL-1b) showed increased expression at all three timepoints. These observations are consistent with the report by Burger et al testing protein levels and showing that blood levels of soluble IL1-ra increase with Copaxone® treatment in patients with MS as well as EAE mice, and that soluble IL1-ra is upregulated by Copaxone® treatment in human monocytes either stimulated with LPS or activated by T cell contact (Burger et al, PNAS 2009).

Copaxone® significantly modulated many validated pathways (Supplementary Table 2). At 6 hours, pathways enriched significantly among upregulated genes included broad categories such as immune response and regulation of immune processes, and more specifically cytokine-cytokine receptor interactions. Other significantly enriched pathways included adhesion; extracellular region; plasma membrane; membrane; response to external stimulus; response to stress; response to wounding; defense response; inflammatory response; and immune system

process, all pathways with broad relevance to the disease process and/or proposed mechanism of action of Copaxone®. Several of these pathways (e.g., extracellular region; immune system process; defense response; regulation of leukocyte activation) were also seen significantly enriched among genes modulated by Copaxone in monocytes obtained from RRMS patients within the first two months of treatment (Thamilarasan, J Neuroinflammation 2013).

2. Gene-level differentiation analysis identifies specific pro-inflammatory markers

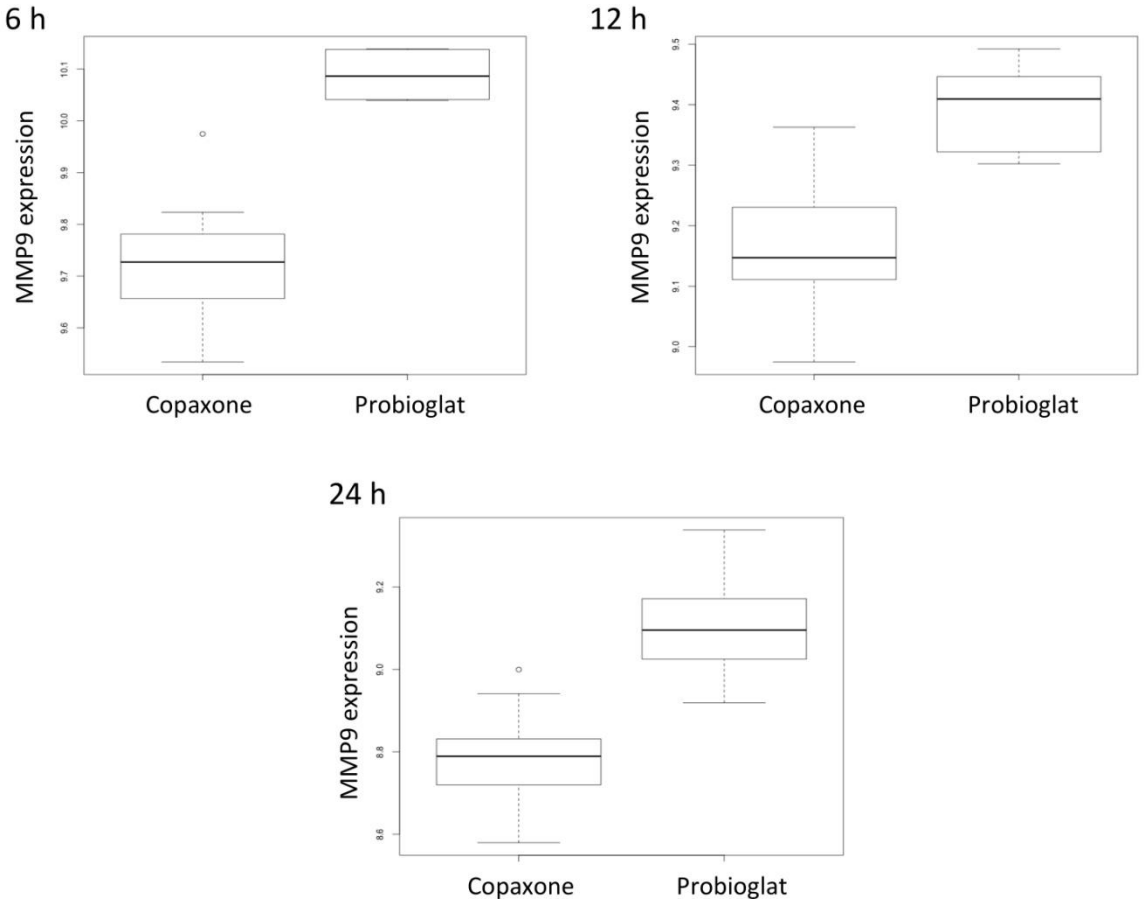
When comparing Probioglat to Copaxone®, significant gene expression differences were seen**. Given the stringent statistical framework employed in this study and the confirmatory results obtained by single-probeset, pathway and independent qRT-PCR analysis, it is striking that differences were observed between Copaxone® and the designed purported generic, Probioglat. Two drugs cannot be said to have identical effects if significant differences are manifest.** Importantly, the significant differences in gene expression observed between Probioglat and Copaxone® were seen in genes tied to highly relevant disease pathoetiology and known Copaxone® mode of action. Bioinformatic analysis of differentially expressed genes (by FDR corrected p value) following Probioglat versus Copaxone® stimulation of human monocytes at 6 hours (Summarized in Table 2, full list in Supplementary Table 6) identified a number of genes tied to important immune system functions, in particular pro-inflammatory signatures. These genes include *CCL5, CCL2, MMP9, MMP1, CXCL10, CD14, ICAM1* and *BIRC3*. Several of these genes have been reported in the literature as modulated by Copaxone treatment in patients.

1. **CCL5** (RANTES) is a key chemokine thought to attract inflammatory immune cells to the CNS, and was significantly upregulated in Probioglat treatment relative to Copaxone® treatment at 6 hours (FDR adjusted p value 0.018 in gene expression analysis; p value 4e-5 in qRT-PCR confirmation). Indeed, an antibody blocking CCL5 was shown to reduce disease metrics including immune infiltration into the CNS in a viral MS model (Glass et al, Immunol Res, 2004). Expression of the CCL5 receptor, CCR5, on Copaxone®-reactive T cells from MS patients was shown to be downregulated by chronic (1 year) Copaxone® treatment (Allie et al, Arch Neurol 2005).

2. **MMP9** (Matrix Metalloproteinase 9) is a protein reported to increase access of immune cells to the CNS by con tributing to disruption of the blood brain barrier (BBB) (Rosenberg et al, The Lancet 2005), and high levels of MMP9 have been associated with MS (Christensen et al, Mult. Scler 2013). MMP9 was upregulated with Probioglat relative to Copaxone® stimulation at 6 hours (FDR adjusted p value 2.8e-6 in gene expression analysis; p value 0.02 in qRT-PCR confirmation). Expression levels of MMP9 at both the mRNA and protein level were increased in immature dendritic cells from MS patients relative to healthy controls (Kouwenhoven et al, J Neuroimmunol 2002). Elevated MMP9 levels were reported in patients with gadolinium-enhancing lesions relative to patients without (Waubant et al, Dis Markers 2006), and MMP9 has been proposed as a biomarker for both MS diagnosis

and progression (Milward et al, J Neuroimmunol 2008). Copaxone®, by contrast, has been reported to inhibit MMP9 expression in healthy human peripheral blood mononuclear cells (PBMC) (Knop et al, Neurology 2013 (Meeting Abstract)). [Figure 11 includes boxplots showing increased expression of MMP9 for Probioglat relative to Copaxone® at multiple timepoints.]

Figure 11. MMP9 is significantly upregulated following stimulation by Probioglat compared to Copaxone® at 6 and 24 hours (FDR adjusted p values for the single MMP9 probeset on the chip, 203936_s_at, are 2.74e-6, 0.098, and 0.004 for the 6, 12, and 24 hours timepoints, respectively).

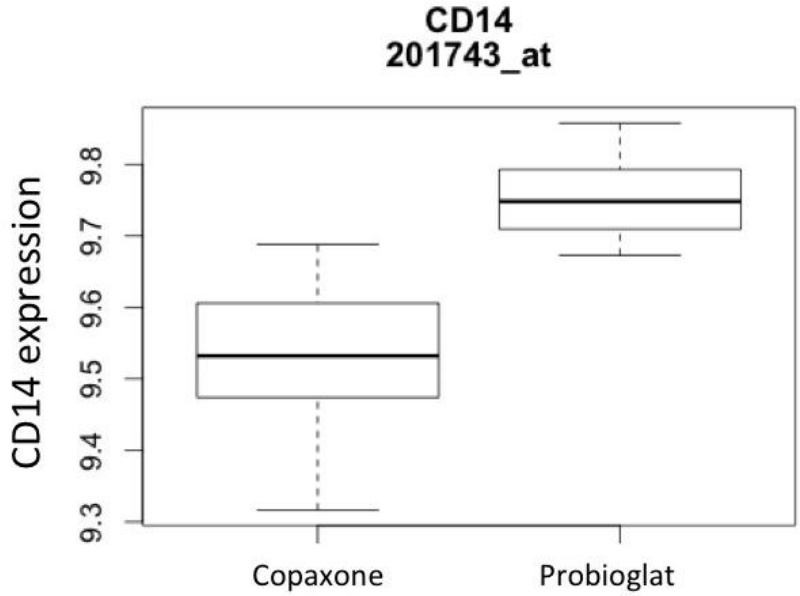


3. **MMP1**, another matrix metalloproteinase, was upregulated after Probioglat stimulation compared to Copaxone® at 6 hours (FDR adjusted p value 0.002 in gene expression analysis; p value 0.02 in qRT-PCR confirmation). Matrix metalloproteinases are known to cleave pro-inflammatory cytokines and chemokines to regulate inflammation (Parks et al, Nat Rev Immunol, 2004). Levels of MMP1 mRNA, as well as secreted MMP1, were observed to be higher in immature dendritic cells from MS patients relative to healthy controls (Kouwenhoven et al, J Neuroimmunol 2002).

4. **CXCL10**, a chemokine, was upregulated by Probioglat stimulation compared to Copaxone® at 6 hours (FDR adjusted p value 0.0006 in gene expression analysis; p value 0.0029 in qRT-PCR confirmation). CXCL10 level in peripheral fluids was previously shown as associated with host immune response, particularly with regard to Th-1 cells (Antonelli et al, Autoimm. Rev., 2014). CXCL10 is involved in recruiting $CD8^+$ and Th1 $CD4^+$ effector T cells to sites of inflammation (Peperzak et al, J Immunol, 2013). A study using monocytes from RRMS patients demonstrated CXCL10 to be increased by Copaxone® therapy within the first two months of treatment (Thamilarasan et al, J Neuroinflammation 2013).

5. **CD14** is a marker of monocyte activation known to enhance inflammatory responses. CD14 was upregulated in human monocytes stimulated by Probioglat versus Copaxone® at 6 hours (FDR adjusted p value 0.006; qRT-PCR not tested). In complex with LPS binding protein (LBP), CD14 interacts with LPS and helps to present it to toll-like receptor 4 (TLR4), activating downstream expression of inflammatory genes via NF-kB (Park et al, Exp Mol Med, 2013). CD14 has also been shown to be a coreceptor for other TLRs, and was demonstrated to be required for induction of proinflammatory cytokines via TLR7 and TLR9 in mouse and human cells in vitro (Baumann et al, J Exp Med, 2010). [Figure 12 includes boxplots showing increased expression of CD14 for Probioglat relative to Copaxone®.]

Figure 12. CD14 expression is significantly higher with stimulation by Probioglat compared to Copaxone® at 6 hours (the single CD14 probeset on the chip is shown, 201743_at).



6. **CARD15** (NOD2), another gene upregulated by Probioglat versus Copaxone® at 6 hours (FDR adjusted p value 0.02; qRT-PCR not tested), is also a key player in the immune response to LPS, participating in activation of NF-kB in response to LPS. Activation of NOD2 by peptidoglycan has been shown to induce CNS demyelination in rats (Natarajan et al, 2013). In addition, a SNP in NOD2 was shown to affect the responses of Th2 and Th17 cells to myelin basic protein (MBP) in MS (Hedegaard et al, 2011).

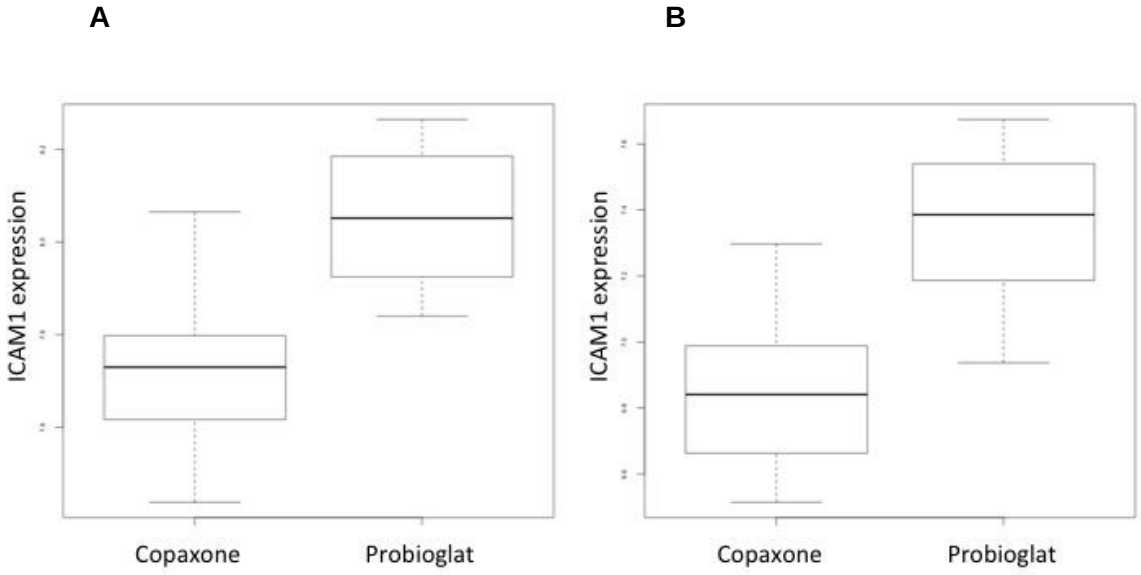
7. **BIRC3** was upregulated by Probioglat relative to Copaxone® at 6 hours (FDR adjusted p value 0.018; qRT-PCR not tested). This gene codes for an Inhibitor of Apoptosis Protein (IAP-1), which in addition to its role in cell survival plays a role in both innate immunity (Bertrand, 2009) and inflammation (Labbe et al, 2011), and has been suggested to have an immunomodulatory effect in autoimmune demyelination (Hebb et al, 2008). IAPs including IAP-1 are required for production of pro-inflammatory cytokines via several different pathways, including TLR4 activation (Tseng et al, 2010) and NOD2 activation by TNF (Kearney et al, JBC, 2012).

8. **CCL2** (MCP-1) is another pro-inflammatory cytokine that was also upregulated by Probioglat relative to Copaxone® at 6 hours (FDR adjusted p value 0.003; qRT-PCR not tested). CCL2 is thought to recruit inflammatory cells into the CNS in EAE and in MS. (Mahad et al, 2006)

9. **ICAM1** was upregulated by Probioglat relative to Copaxone® at 6 hours (FDR adjusted p value 0.004; qRT-PCR not tested). ICAM1 is an adhesion molecule that

plays a key role in inflammatory processes by promoting leukocyte adhesion to the endothelium of the vascular wall, and is known to have an important role in inflammatory cell infiltration into the CNS in both EAE and MS (Mycko et al, Ann. Neurol. 1994). In mice null for ICAM1, T cells produced significantly less IFNγ and showed much less infiltration into the spinal cord (Bullard et al, J Immunol, 2007). In PBMC from RRMS patients, ICAM1 levels were higher versus healthy controls, and chronic treatment with Copaxone® affected surface ICAM1 levels in multiple immune cell types (Sellner et al, Clin Exp Immunol 2013). [Figure 13 includes boxplots showing increased expression of ICAM1 for Probioglat compared to Copaxone stimulation.]

Figure 13. Both present ICAM1 probesets are significantly upregulated following stimulation by Probioglat compared to Copaxone® at 6 hours (A: probeset 202637_s_at; B: probeset 202638_s_at).



3. Pathway-level differentiation analysis identifies inflammation as a key affected function

The genes significantly upregulated (FDR adjusted p value < 0.05) in Probioglat relative to Copaxone® treatment at 6 hours were found to be enriched significantly (Benjamini corrected p value < 0.05) for 106 pathways annotated in the GO (Biological Process, Cellular Component, and Molecular Function) and Kegg databases (The Gene Ontology Consortium. Gene ontology: tool for the unification of biology, Nat. Genet., May 2000; Kanehisa et al, KEGG: Kyoto

Encyclopedia of Genes and Genomes, NAR, 2000) (Figure 9 above). These include immune system process (GO:0002376), response to lipopolysaccharide (LPS) (GO:0032496), and immune response (GO:0006955) pathways (Benjamini corrected p values 1.5e-5, 8.7e-4, and 3.3e-4, respectively). Several of these pathways are relevant to inflammation (e.g., regulation of inflammatory response (GO:0050727) and regulation of tumor necrosis factor production (GO:0032680), Benjamini corrected p values of 0.015 and 0.028, respectively). As another example, NOD-like receptor signaling (hsa04621, Benjamini corrected p value 0.027) regulates inflammatory and apoptotic responses. The response to LPS pathway (Figure 10 above) includes the genes CD14, CCL5, THBD, CARD15, NFKBIA, and CCL2, all upregulated in Probioglat treatment versus Copaxone® at 6 hours. This pathway was also significantly enriched among probesets upregulated by Copaxone® treatment at 6 hours, though with a lower enrichment score (14.8 vs 2.7) and higher p value (0.00087 vs 0.036). The strong enrichment induced by Probioglat relative to Copaxone® of this prototypical pro-inflammatory pathway raises concerns for the potential health consequences of its use in MS patients.

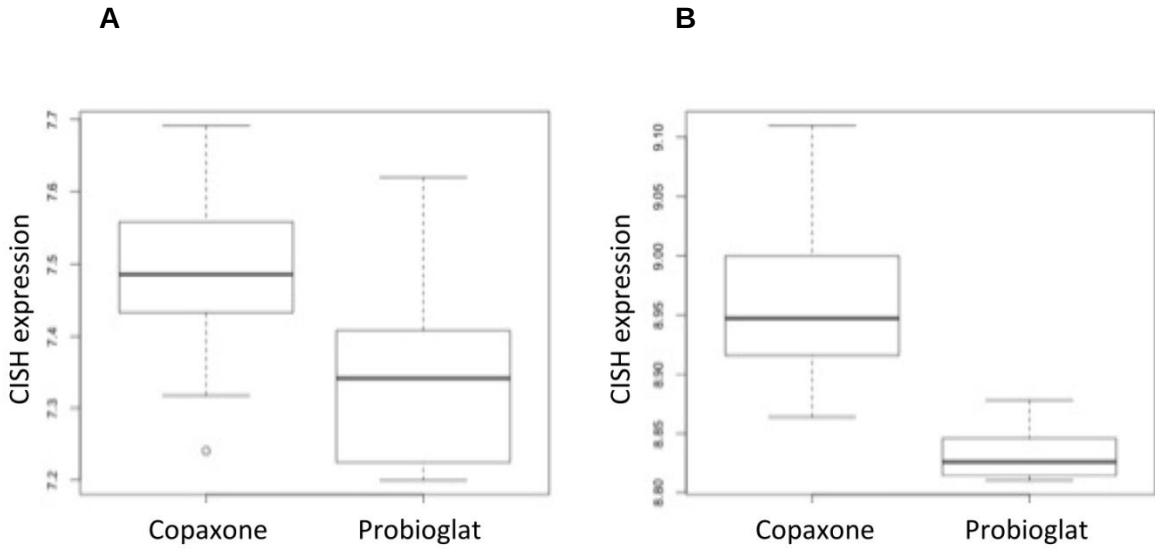
Interestingly, about half of the pathways (58 out of 114) significantly enriched (Benjamini corrected p value < 0.05) among genes upregulated by Copaxone® treatment versus mannitol control at 6 hours were also significantly enriched among genes upregulated by Probioglat relative to Copaxone® treatment. This indicates that many of the effects of Copaxone® treatment were accomplished to a differing extent by Probioglat. What this would imply for efficacy in patients is unclear, and would need to be evaluated in the appropriate setting (e.g., a clinical trial). An additional 48 pathways were significantly enriched among genes upregulated by Probioglat relative to Copaxone® (and not modulated by Copaxone® relative to mannitol control). These include pathways relevant to inflammation, such as response to molecule of bacterial origin (GO:0002237), regulation of tumor necrosis factor production (GO:0032680) and NOD-like receptor signaling pathway (hsa04621), as well as other immune pathways including regulation of lymphocyte mediated immunity (GO:0002706) and B cell proliferation (GO:0042100).

4. Effects on anti-inflammatory genes following stimulation by Probioglat compared to Copaxone®

As discussed above, a number of pro-inflammatory genes and pathways were shown to be significantly upregulated by Probioglat as compared to Copaxone®. At the same time, several anti-inflammatory genes were downregulated by Probioglat stimulation in comparison with Copaxone® at 6 hours.

1. **CISH**, also known as **SOCS** (Suppressor of Cytokine Signaling), was downregulated in Probioglat relative to Copaxone® at 6 hours (FDR adjusted p value 0.03). A closely related protein, **SOCS3**, has been shown in myeloid cells to protect from EAE, the mouse model of MS, via deactivating neuroinflammatory responses (Qin et al, PNAS 2012). Figure 14 shows boxplots for both present probesets for this gene, affected in the same direction.

Figure 14. CISH is downregulated following stimulation by Probioglat compared to Copaxone® at 6 hours (Both present probesets are shown. A: probeset 223961_s_at; B: probeset 223377_x_at).



2. **HSPD1**, also known as **HSP-60** (heat shock 60kDa protein 1), was downregulated in Probioglat relative to Copaxone® at 6 hours (FDR adjusted p value 0.01). Zanin-Zhorov et al (2006) showed that HSP60 as well as synthetic peptide derived from HSP60 acted as co-stimulators of Tregs through the TLR2 pathway. Tregs are immune regulatory cells that inhibit lympho-proliferation and IFNG and TNF secretion by pro-inflammatory T cells. Zanin-Zhorov et al concluded that HSP60 can downregulate adaptive immune responses by upregulating Tregs. Thus, downregulation of HSPD1 may result in less inhibition of immune response by Probioglat compared to Copaxone®.

It should be noted, however, the anti-inflammatory cytokine IL10, known to be relevant to the Copaxone® mechanism of action, was also expressed more highly with Probioglat relative to Copaxone® treatment at 6 hours (FDR adjusted p value 0.005). The same observation holds for another gene at 6 and 12 hours, PRDM1 (Blimp1) (FDR adjusted p value 0.0006 and 7.7e-6, respectively), that when deleted results in inflammatory pathology (Chiang et al, PNAS 2013). Blimp1 is a target of FOXP3 and is needed for production of IL10 by Tregs; its expression can also be induced by IL2 and proinflammatory cytokines in Tregs (Cretney et al, Nat Immunol. 2011). However, it is not clear what these observations would imply for APCs such as monocytes. It is possible that higher Blimp1 could be an attempted protective response to a higher inflammatory milieu.

e. Overall biological signatures and their relevance to the comparison of Copaxone® with purported generic

The complex picture described here underscores a key point about the intricate relationships between immune processes, effect of treatment on each component of the associated pathways and the unique response registered by each immune cell type. We do not recommend any particular panel of genes to be used to differentiate Copaxone® and differently manufactured glatiramoids. As these experiments combined with previous evidence from other systems and cell types shows [Bakshi et al; Towfic et al], the nature of the differences is dependent on the biological context of the tested model, but consistently in each system, differences are observed between Copaxone® and differently manufactured glatiramoids. Further, it has been consistently observed that many of these differences affect molecules relevant to drug mechanism of action and to MS disease pathoetiology, particularly with regard to pro- versus anti-inflammatory signatures.

The importance of these findings is underscored by the fact that, as discussed above (in the Introduction section), clinical effects of the introduction of Probioglat are observed (Table 1; Figure 1). The adverse events reported included severe injection site reactions that could be especially relevant to the present study's observations of increased expression of inflammatory mediators at an early treatment timepoint of 6 hours. Especially in light of these clinical observations, the gene expression differences observed in this study between Copaxone® and Probioglat warrant careful further study to ensure efficacy and safety for patients, in a meaningful setting. Carefully designed and interpreted gene expression studies illuminating each of these levels of gene, pathway and immunological cell type could assist in this endeavor. Such studies might also help to indicate whether a clinical trial is necessary.

f. Summary

In summary, the impact of Copaxone®-treatment on the human THP-1 monocyte cell line was measured at several time points of exposure as part of Teva's latest efforts to characterize Copaxone®'s complex mechanism. At the 6 hour timepoint, over 6,500 genes were significantly (FDR < 0.05) modulated by Copaxone® (compared to mannitol control). The large number of genes makes it challenging to design a simple gene-panel signature of Copaxone® to use as a quality control measure for comparing Copaxone® lots. However, having a well-powered experiment based on genome-wide gene expression arrays to measure the biological impact of Copaxone® allowed the characterization of some of Copaxone's mechanism in monocytes. As discussed in the Copaxone® mechanism of action section, Copaxone®'s impact on monocytes is consistent with what is already well known in the literature (e.g., IL10 induction or IL1RN induction, both shown to be upregulated by Copaxone® in the literature).

4. Analysis of additional purported generics reveals limitations of focused gene panels

Certain methods have been publicly described in patent application filings by manufacturers seeking to develop purported generics (including International Publication Number WO2008/157697 by Momenta Pharmaceuticals, Inc.), suggesting that glatiramoids can

be compared by analyzing a panel comprising only a small subset of proteins and/or the genes coding for those proteins. To evaluate the effectiveness of such comparisons, we applied the same methods used to study Probioglat and Copaxone® in human monocytes to also study purported generics Escadra (Raffo, Argentina) and Glatimer (Natco, India). Both purported generics modulated many genes to a significantly different extent than Copaxone®. These differentially expressed genes included genes with relevance for MS. For instance, **both Natco and Escadra differed significantly from Copaxone® in expression of CD9, a component of myelin and a marker of myelinogenic progenitor cells** (Sim et al, Nature Biotechnology, 2011). As another example, **Escadra differed significantly from Copaxone® in expression of CD44, the receptor for hyaluronan which accumulates in demyelinated lesions** (Back et al, Nature Medicine, 2005). Despite significant differences such as these between Copaxone® and the purported generics in expression of biologically relevant genes, **when we examined only the small subset of genes coding for proteins identified in the Momenta patent, there were no significant differences in expression (see Figure 15). This demonstrates that methods focusing on only a small selected subset of genes may miss important differences between two glatiramoids.**

Figure 15. Significant gene expression differences are observed between Copaxone® and the purported generics Natco and Escadra in many genes, including several relevant to MS, but not in the genes for a panel of proteins proposed in Momenta's patent.

Gene expression of proteins in Momenta's patent:

	Natco	Escadra
IFNG*		
IL6*		
IL1B		
IL10		
IL12p70		
TNF alpha		
ICAM1		
MMP2		
TNFR1		
TNFR2		
TIMP1		
MMP9		
IP10*		
MCP1		
MDC*		
I309*		
IL8		
MIP1A		
RANTES		
TARC*		
ITAC*		
MIG*		
IL1A*		
IL2*		
IL4*		
IL13*		
IL17A*		
IL17B*		
IL17C*		
IL17D*		
IL17F*		
IL18		
IL23		
LTA*		

Gene expression of proteins not in Momenta's patent:

	Natco	Escadra
ANXA1		
ARRB2		
BEAN		
BIN1		
BIN1		
C13ORF31		
C14ORF10		
C1ORF51		
C1ORF63		
C1ORF63		
CBR4		
CD36		
CD44		
CD44		
CD44		
CD44		
CD9		
CFP		
COL6A1		
CRIP2		
DAB2		
EPB41		
Fam119a		
FGR		
FOXO3B		
GATA2		
HSD11B1		
HSPD1P6		
KIAA0907		
LOC100506233		
LOC387790		

	Natco	Escadra
MCM6		
MMP1		
MPEG1		
MS4A4A		
MTSS1		
MYB		
OLIG1		
PCMTD1		
PLD1		
PPP4R2		
PRDM1		
RBM6		
SNX27		
SOD2		
STATH		
STK4		
STX7		
TAF15		
TARP		
TIA1		
TMF1		
TREM1		
TRGC2		
TRGC2		
TRGC2		
TXNDC11		
UBN2		
ZCCHC7		

* probeset called absent

Adj. p < 0.05 compared with Copaxone

Adj. p > 0.05 compared with Copaxone

5. Integrated Analysis of Copaxone®'s Mechanism of Action: A Data Driven, Genome-Wide Approach Spanning Multiple Species and Cell Types

As part of Teva's commitment to furthering the understanding of Copaxone®'s mechanism of action, analyses were conducted to elucidate the gene expression changes induced by Copaxone® in the following systems:

1) primed, ex vivo mouse splenocytes;

2) THP-1 human monocyte cell line; and

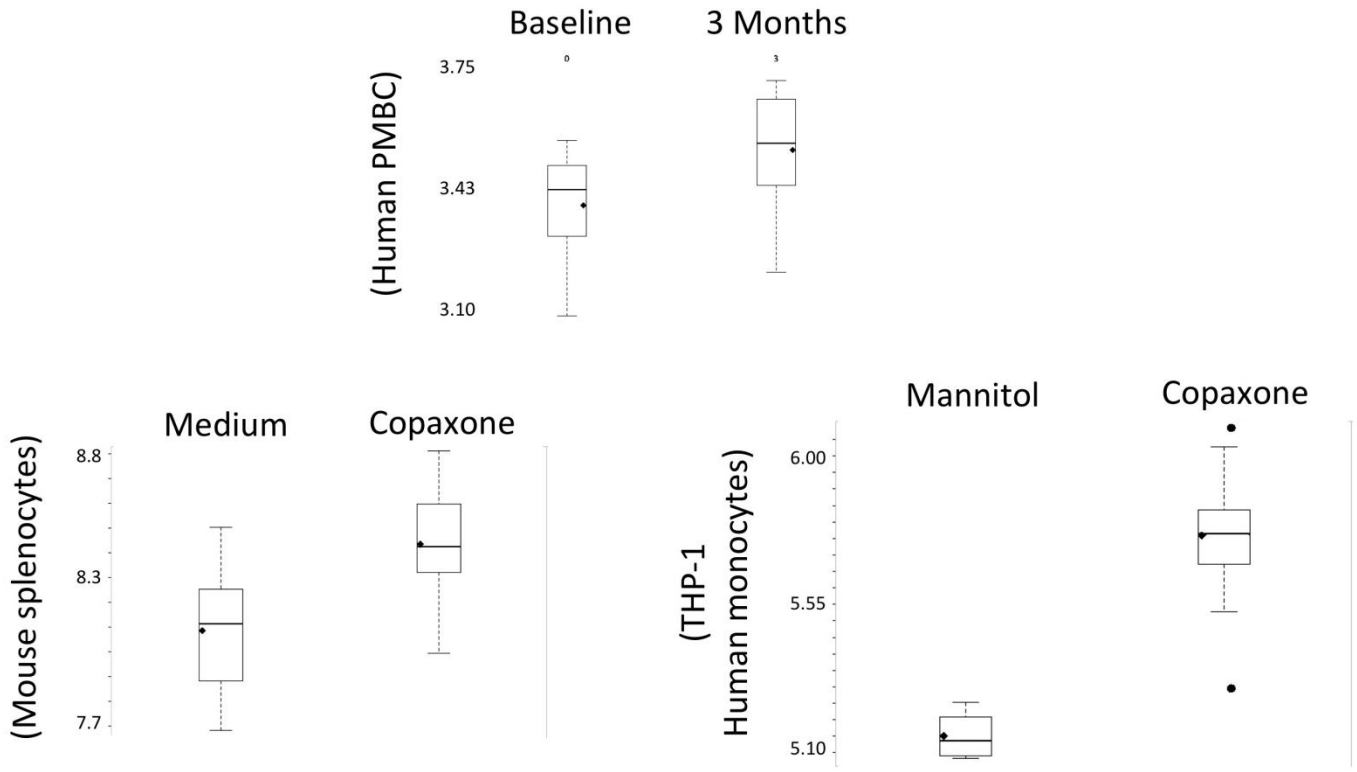
3) samples from MS patients.

Genes, pathways and immune cell types modulated by Copaxone® were investigated, in order to determine which aspects of Copaxone®'s mechanism were observed across all systems utilized, and which were detectable only in certain systems, but not others.

Genome-wide expression profiles in cells from three different datasets in two different species (human, mouse) were studied. LIMMA was utilized to identify a genome-wide list of differentially expressed genes induced by Copaxone® in the primed and ex vivo stimulated mouse splenocytes, as well as in the THP-1 human monocyte cell line. Repeated-measures ANOVA was utilized to find a genome-wide list of genes modulated by Copaxone® in treated MS patients. Advanced enrichment algorithms were then applied to elucidate the pathways and cell types modulated by Copaxone®.

Upregulated expression of the IL-10 gene, a key indicator of the well-studied Th2-shift induced by Copaxone®, was consistently demonstrated in all 3 systems (mouse splenocytes, human monocytes and MS patient PBMCs) [Figure 16]. Copaxone® induces an anti-inflammatory effect, mediated by secretion of IL-4, IL-10, and other anti-inflammatory cytokines. This effect involves both a shift in T cell populations (from pro-inflammatory Th1 to anti-inflammatory Th2) and a shift from monocyte production of IL12 to anti-inflammatory IL10. For example, in vitro Copaxone® treatment increased the proportion of IL10-producing Treg cells in blood from MS patients [Putheti, J Neuroimmunol 2003]. Dendritic cells exposed to Copaxone® during maturation increased their production of IL10 [Vieira et al, J. Immunol 2003], monocytes from mice treated with Copaxone® secreted more IL10 than monocytes from untreated mice [Weber et al, Nat Med 2007], and monocytes isolated from MS patients treated with Copaxone® were shown to upregulate IL10 relative to untreated patients [Kim et al, J Immunol 2004].

Figure 16. Upregulation of IL10 by Copaxone® treatment is consistent in all three studies



The genes modulated by Copaxone® treatment in multiple studies were examined for enrichment in particular immunological cell types. 39 genes were modulated significantly by Copaxone® in all three studies [Figure 17 and Supplementary Table 8]. These genes were significantly enriched for various immunological cell types, including B cells, eosinophils, and megakaryocytes [Table 5].

Figure 17. Overlap of genes significantly modulated by Copaxone® across studies in three model systems

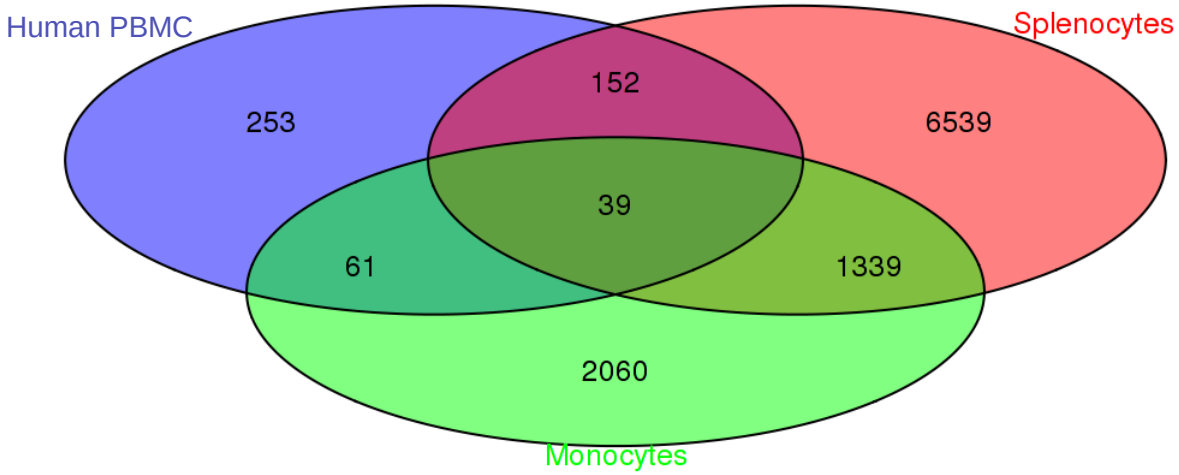


Table 5. Immunological cell type enrichment results for genes modulated by Copaxone® treatment in all three studies

Dataset Name	Score	p.val	adj.p.val	Genes in list >= threshold
BCELLA1.rnk	68.5289498	0.00071035	0.01349673	VAV3,DTX4,TSPAN13,IGHM,SETBP1
BCELLA2.rnk	64.9203176	0.00061785	0.01349673	TSPAN13,IGHM,SETBP1,TNFSF9
EOS2.rnk	63.3972511	0.00330909	0.03450189	TSPAN13,SETBP1
MEGA1.rnk	54.913734	0.00363178	0.03450189	TSPAN13,TPM1
CMP.rnk	61.9612007	0.00582546	0.04427349	TSPAN13

The 39 genes modulated by Copaxone® treatment across model systems represent a small percentage of the total number of genes modulated in each system (8% of genes modulated by Copaxone® treatment in human PBMC; 1% in human monocytes; 0.5% in mouse splenocytes).

In addition to the shared induced effects discussed above, each system and platform clearly captured different aspects of Copaxone®'s impact on the immune system. In mouse splenocytes, genes associated with FOXP3+ regulatory T cells (Tregs), B cells, T cells in general, macrophages, and dendritic cells were significantly modulated upon ex vivo stimulation with Copaxone® after prior inoculation (Table 6). In human monocyte (THP-1) cells, upregulated genes were associated with monocytes along with NK cells, dendritic cells, and granulocytes (Table 7). In human PBMCs, genes associated with immune cell types were modulated early in treatment (by month 3), including certain cell types affected in prior systems, but also distinct cell types, such as megakaryocytes and myeloid progenitors [Table 8].

Table 6. Immunological cell type enrichment for genes modulated by Copaxone® treatment in mouse splenocytes

a) Upregulated (top 20 results)

Dataset Name[23]	Score	p.val	adj.p.val
SC.MEP.BM.rnk	641.2372079	0	0
T.8Eff.Sp.OT1.12hr.LisOva.rnk	683.0376678	0	0
T.8Eff.Sp.OT1.48hr.LisOva.rnk	587.7303361	0	0
T.DPbl.Th.rnk	659.3284877	0	0
T.ISP.Th.rnk	584.8660167	0	0
preB.FrC.BM.rnk	620.1611981	0	0
proB.FrBC.FL.rnk	595.3446445	0	0
DC.LC.Sk.rnk	709.8843317	2.89E-15	6.96E-14
NK.H..MCMV1.Sp.rnk	770.77198	7.11E-15	1.52E-13
DC.103.11b..PolyIC.Lu.rnk	704.9643794	1.44E-14	2.65E-13
NK.MCMV1.Sp.rnk	793.3059033	1.51E-14	2.65E-13
T.8Eff.Sp.OT1.24hr.LisOva.rnk	661.8125467	5.97E-14	9.61E-13
B.GC.Sp.rnk	602.4630175	1.01E-12	1.39E-11
Tgd.vg2.24ahi.e17.Th.rnk	619.9621246	9.88E-13	1.39E-11
DC.103.11b.24..Lu.rnk	738.2608372	8.91E-12	1.15E-10
T.4FP3.25..AA.rnk	697.5960229	2.76E-11	3.14E-10
Tgd.vg3.24alo.e17.Th.rnk	620.789896	2.72E-11	3.14E-10
proB.FrA.FL.rnk	578.5853958	7.17E-11	7.69E-10
preT.DN3B.Th.rnk	567.9618687	1.64E-10	1.67E-09
preT.DN3.4.Th.rnk	560.7279837	2.96E-10	2.86E-09

[23] All immunological cell type terminology in Tables 5-7 as defined via Immgen (http://www.immgen.org/).

b) Downregulated (top 20 results)

Dataset Name	Score	p.val	adj.p.val
GN.Arth.BM.rnk	1217.738372	0	0
SC.CDP.BM.rnk	1077.505969	0	0
T.4SP24int.Th.rnk	1040.246786	0	0
T.8Nve.Sp.OT1.rnk	1095.134864	0	0
proB.CLP.FL.rnk	1115.01089	0	0
GN.BM.rnk	1212.480897	1.11E-16	3.57E-15
GN.Bl.rnk	1184.87043	6.66E-15	1.84E-13
GN.UrAc.PC.rnk	1145.080376	5.87E-14	1.37E-12
GN.Thio.PC.rnk	1197.163456	6.39E-14	1.37E-12
GN.Arth.SynF.rnk	1160.159783	2.72E-11	5.25E-10
DC.IIhilang.103.11blo.SLN.rnk	1112.24759	5.07E-08	8.90E-07
DC.IIhilang.103.11b..SLN.rnk	1151.229363	9.94E-08	1.60E-06
DC.8.4.11b..SLN.rnk	1116.686609	1.86E-07	2.77E-06
proB.CLP.BM.rnk	1181.133013	1.35E-06	1.86E-05
Mo.6C.II..BM.rnk	1094.697148	1.71E-06	2.20E-05
DC.103.11b..LuLN.rnk	1151.971571	2.47E-06	2.98E-05
SC.GMP.BM.rnk	1340.719659	1.56E-05	0.000164843
SC.MDP.BM.rnk	1206.224359	1.56E-05	0.000164843
Mo.6C.IIint.Bl.rnk	1106.765118	1.62E-05	0.000164843

Table 7. Immunological cell type enrichment for genes upregulated by Copaxone® treatment in human monocytes

Dataset Name	Score	p.val	adj.p.val
MONO2.rnk	108.0701335	0	0
NKA1.rnk	97.70225302	2.00E-15	3.80E-14
MONO1.rnk	104.5121531	8.28E-13	1.05E-11
GRAN2.rnk	97.10283117	1.17E-09	1.11E-08
GRAN3.rnk	91.49890345	1.27E-07	9.40E-07
DENDA2.rnk	100.4177838	1.48E-07	9.40E-07
DENDA1.rnk	111.2455747	7.78E-05	0.000422143
EOS2.rnk	94.29494842	0.000223937	0.001063701
MEGA2.rnk	101.6956549	0.007442566	0.031424168

Table 8. Immunological cell type enrichment for genes modulated by Copaxone® treatment in human PBMC

a) Upregulated, by cluster resulting from consensus k-means clustering on gene expression profiles (as described in methods). All clusters of genes that resulted in significant cell type enrichment are included.
Cluster 0:

Dataset Name	Score	p.val	adj.p.val	Genes in list >= threshold
MEGA2.rnk	32.42631137	1.24E-12	4.70E-11	PTPN18,ILK,RAB27B,FHL1,EPOR,FYN,MAX,PARVB,TUBB1,TPM1,VCL,TPM4

Cluster 2:

Dataset Name	Score	p.val	adj.p.val	Genes in list >= threshold
PRE_BCELL3.rnk	57.93896297	3.98E-08	1.51E-06	IGL@,TOP2A,NUSAP1,IRF4,IGHM,IGL@,BIRC5
ERY5.rnk	64.22953395	9.88E-07	1.88E-05	IGL@,TOP2A,NUSAP1,IGHM,MYL4,MKI67,IGL@,H2AFX,RPIP8,GYPC,BIRC5
ERY2.rnk	32.83132369	8.43E-05	0.001067894	BUB1B,TOP2A,NUSAP1,MCM4,TUBB,MYL4,CDC6,BIRC5
ERY4.rnk	69.43612767	0.000141687	0.001346024	TOP2A,NUSAP1,TUBB,MYL4,MKI67,CDC2,RPIP8,GYPC,BIRC5
ERY3.rnk	84.61769579	0.000286865	0.002180171	BUB1B,TOP2A,NUSAP1,TUBB,MYL4,MKI67,CDC2,RPIP8,GYPC,BIRC5
GRAN1.rnk	55.17000868	0.000557705	0.003532132	IGHG1,IGL@,TOP2A,NUSAP1,IRF4,IGHM,IGL@,BIRC5
EOS2.rnk	62.69263216	0.002286284	0.012411257	IGL@,IRF4,IGHM,IGL@
BASO1.rnk	87.29704767	0.003219714	0.013594346	IGL@,IGHM,IGL@
ERY1.rnk	28.25494881	0.003043224	0.013594346	BUB1B,NUSAP1,MCM4,TUBB,MS4A2,BIRC5
MEP.rnk	30.5446045	0.009387769	0.035673524	TOP2A,NUSAP1,MCM4,TUBB,MS4A2,BIRC5

Cluster 4:

Dataset Name	Score	p.val	adj.p.val	Genes in list >= threshold
MEGA2.rnk	64.4584783	4.41E-12	1.67E-10	PARD3,GNB5,C5ORF4,LIMS1, ACTN1,ITGB3,ITGA2B,GPX1,IGF2BP 3,CLU,LTBP1
MEGA1.rnk	38.04817949	4.66E-09	8.86E-08	HMGA2,LIMS1,ACTN1,ITGB3, ITGA2B,GPX1,IGF2BP3,LTBP1
ERY2.rnk	47.24788403	4.70E-06	5.96E-05	HMGA2,LIMS1,ACTN1,ITGB3, ITGA2B,IGF2BP3,CLU,LTBP1
GMP.rnk	33.12681006	0.000142682	0.001355477	ACTN1,GPX1,IGF2BP3,LTBP1
HSC3.rnk	45.40525942	0.000287455	0.002184658	HMGA2,LIMS1,GPX1,IGF2BP3, HIST1H3D,LTBP1,INPP4B
ERY5.rnk	73.41821315	0.000980846	0.006212027	CLCN3,C5ORF4,ITGB3,GPX1, IGF2BP3,LTBP1
CMP.rnk	23.1944575	0.002214239	0.010517637	HMGA2,IGF2BP3
ERY4.rnk	77.37714483	0.001966408	0.010517637	RAB6B,CLCN3,C5ORF4,GPX1, IGF2BP3,LTBP1
ERY1.rnk	45.00063371	0.002587112	0.010923363	HMGA2,GPX1,IGF2BP3,MALL, LTBP1
ERY3.rnk	90.0166825	0.009061135	0.031302103	RAB6B,CLCN3,C5ORF4,GPX1, IGF2BP3,LTBP1
GRAN2.rnk	35.17942767	0.008750011	0.031302103	ACTN1,ITGB3,GPX1,IGF2BP3, LTBP1

b) Downregulated, by cluster resulting from consensus k-means clustering on gene expression profiles (as described in methods)
Cluster 0:

Dataset Name	Score	p.val	adj.p.val	Genes in list >= threshold
BCELLA2.rnk	-25.76679646	0.000420072	0.015962749	ITSN1,ZNF365,GYG2
BCELLA1.rnk	-19.11170698	0.002736809	0.025999686	ITSN1,ANK3,ZNF365,GYG2,EXTL2
BCELLA3.rnk	-20.11301566	0.00138472	0.025999686	ITSN1,ZNF365,GYG2
BCELLA4.rnk	-21.51318153	0.00253799	0.025999686	ITSN1,LILRA4,GYG2,EXTL2

In sum, the genome-wide gene expression data collected by Gurevich et al as part of the FORTE clinical trial indicated that there were over 1300 probesets (over 1200 genes) modulated by Copaxone® based on patient PBMC's. The diversity of the cell types enriched from the list of 1200 genes (B cells, T cells, monocyte progenitors, megakaryocytes) indicates the wide-ranging effects of Copaxone on the immune system. Similar to what was observed in the splenocyte data, it is difficult to define a small panel of genes to use as quality-control measures against a given Copaxone® lot due to the wide-ranging effect of the drug. Using genome-wide gene-expression arrays, we compared the gene expression from the human PBMC data, mouse splenocytes and human THP-1 monocyte cell line and discovered that **although there are genes that are consistently modulated by Copaxone® across all those experimental systems (e.g., IL10), some gene-expression signatures and cell types (e.g., B-cells) were seen only in one system (e.g., human PBMC data) but not as clearly in the other systems (e.g., monocytes and splenocyte data)**. Looking at genome-wide gene expression signatures can yield a good characterization of the impact of Copaxone® on a single system (e.g., THP-1 monocytes) but **well-powered experiments in multiple systems are necessary to fully characterize the systemic biological impact of Copaxone®.**

6. Overarching Conclusion

In summary, as part of Teva's ongoing commitment to better understand Copaxone®, Teva has studied (and continues to study) its effect at the **level of gene expression across the entire genome** (unbiased, without prior hypothesis about the genes for which expression pattern may be altered and without choosing which genes to focus on or study) in a variety of model systems, including mouse splenocytes, human monocytes, and PBMC from MS patients. **The genome-wide approach is critical, because two glatiramoids can appear identical based on**

a small panel of genes, yet differ significantly in their impact on other genes that are potentially highly relevant to safety and/or efficacy. **Using multiple model systems is equally critical, since Copaxone® significantly impacts a variety of cell types**. The unbiased approach allows identification of genes and pathways with subtle, yet robust, differential expression patterns following stimulation by different glatiramoids in different experimental contexts. Each of these model systems creates an immunological context that captures different aspects of Copaxone®'s mechanism of action, such that **no single cell type or system tested was sufficient to fully characterize the biological impact of this complex drug.**

The fact that differences were observed for each of the systems tested despite the careful experimental design and stringent statistical methodology clearly indicate that the statistically significant differences, and biologically meaningful associations (e.g., related to the disease biology or any of the drug's known or putative targets and downstream pathways), warrant further studies and careful characterization. **It is further demonstrated that genome-wide expression methodologies can be utilized as key components of the evaluation of candidate generic versions of the class of NBCDs, following the rationale that two drugs that have identical activities in biological systems should not induce statistically observable and biologically enriched differences when compared against each other.**

In conclusion, Copaxone® modulates many pathways and immune cell types, which cannot be adequately characterized by studies focused on a specific subset of genes or a single cell type. Multiple systems and genome-wide methods are necessary to properly study Copaxone®'s complex interactions with the immune system. To this end, Teva continues to study Copaxone® and other glatiramoids in order to advance scientific understanding of these complex drugs and ensure the safe and efficacious treatment of MS patients worldwide.

4. Methods

For methods used in mouse studies, please refer to publications Bakshi et al and Towfic et al (Exhibits 12 and 5, respectively).

a. Methods for Human Monocyte Studies

1. Experimental design

Cells from a human monocyte cell line (THP-1) were stimulated with either branded glatiramer acetate (Copaxone®), purported generics including Probioglat (by ProbioMed), or vehicle control (mannitol) for 6, 12, or 24 hours. RNA was extracted and expression profiled across the entire genome using the Affymetrix Human Genome U133 Plus 2.0 chip, interrogating a total of over 47,000 transcripts. Three batches of Copaxone® and one batch of Probioglat were comparatively tested in six replicates each. Key identified genes were independently evaluated for level of gene expression by quantitative Real-Time PCR of samples collected in the same experiments. Of the three time points tested, we sought to identify the time point reflecting the greatest impact of treatment in this model system. Examining the number of genes modulated by Copaxone® relative to the mannitol control, we found that the 6 hour time point demonstrated the largest number of genes significantly modulated by Copaxone® (6,890 with an FDR-adjusted p <

0.05), over 2-fold more than at 12 hours (3,118 with FDA-adjusted $p < 0.05$) and nearly 4-fold more than at 24 hours (1,791 with FDR-adjusted $p < 0.05$). We therefore focused on the 6 hour time point for subsequent analyses.

2. Power analysis

Using the R statistical package ssize.fdr, power calculations were performed to determine the number of samples needed to detect differentially expressed genes with a fold-change between treatments of as low as 1.3 with 80% power. Based on the results of these power calculations, the experiment was designed to include six replicates of each condition. The order in which the samples were processed was randomized with respect to treatment and stimulation time in order to avoid creating confounding batch effects.

3. Batch correction

Correction for batch variation was performed using ComBat (Johnson et al, Biostat, 2007), as implemented in the SVA R package (Leek JT, Johnson WE, Parker HS, Jaffe AE, Storey JD (2013) sva: Surrogate Variable Analysis. Available: http://www.bioconductor.org/packages/release/bioc/html/sva.html). Treatment labels were added as covariates to the batch correction in order to preserve relevant treatment effects. Briefly, ComBat is an empirical Bayesian approach utilizing location and scale metrics across several genes to adjust for batch effects in datasets, even datasets containing small sample sizes. Principal Component Analysis (a multivariate approach) showed that the main effect in the first principal component remained due to treatment effects after batch correction.

4. Differential expression analysis

Differentially expressed probesets were identified across conditions using linear models for microarray data (LIMMA; Smyth, G. K. (2004)), a standard R Bioconductor package. Linear models and empirical Bayes methods for assessing differential expression in microarray experiments. Statistical Applications in Genetics and Molecular Biology 3, No. 1, Article 3). To compare Copaxone® and Probioglat, comparisons were corrected to compare each treatment relative to mannitol control ([Copaxone® versus mannitol] was compared via LIMMA to [Probioglat vs mannitol]). Probesets were filtered by calls of presence on the chip for the relevant samples in the comparison (to be considered present at a given timepoint, a probeset was required to have on average a call of present or marginal across the relevant samples at that timepoint). Probesets were mapped to genes using the annotation available for the U133 Plus 2.0 chip from Affymetrix. FDR adjusted p values reported for genes represent the lowest FDR adjusted p value for present probesets for that gene.

5. Pathway enrichment analysis

Upregulated and downregulated genes were analyzed separately for pathway enrichment, using DAVID (Huang et al, Nucleic Acids Res 2009). Pathway enrichment results were visualized using volcano plots, plotting either –log adjusted p values or untransformed adjusted p

values versus enrichment scores for the pathways. For comparisons between Copaxone® and Probioglat, upregulated or downregulated genes with FDR-adjusted p values < 0.05 were used for pathway enrichment.

DAVID runs were conducted May 21, 2014. Please note that the GO databases are updated daily (as noted on the GO site: http://www.geneontology.org/GO.downloads.ontology.shtml) and therefore performing the same enrichments on the same genesets may yield slightly varying results depending on the run date. Thus, the pathway p values may change slightly between runs conducted at different times; the overall picture of enriched pathways, however, is expected to remain consistent.

6. qRT-PCR analysis

Key genes identified by differential expression analysis were assayed using qRT-PCR. RNA was utilized from each of 6 biological samples for each treatment (Copaxone® and Probioglat) and 15 technical replicates were performed for each sample (a total of 90 observations per transcript per treatment). Since three Copaxone® batches and one Probioglat batch were available, a total of 360 observations from each transcript were evaluated. To evaluate the data, the $2^{-\Delta\Delta Ct}$ approximation was utilized with GAPDH as reference transcript and vehicle control (mannitol) as calibrator. A one-sided t-test with unequal variance was used to compare the RNA expression from the two treatments.

b. Methods for multi-study comparison of Copaxone treatment effects

Mouse splenocyte studies utilized a subset of data published in Towfic et al (2013) from mouse splenocytes, consisting of RNA samples from Copaxone-treated splenocytes (34 samples, each with 2 technical replicates) and medium (15 samples, each with 2 technical replicates).
Human monocyte studies utilized RNA samples from Copaxone-treated THP-1 monocytes. 18 samples (3 treatments with 6 replicates each) were compared against mannitol controls (6 replicates) at 6, 12 and 24 hour timepoints. This analysis focused on the 6 hour timepoint.

c. Methods for studies using MS patient data

The patient study utilized in section II.B.4 included a subset of RRMS patients treated with Copaxone from the FORTE clinical trial with time-series PBMC expression profiling (Affymetrix U133A-2 chip, 22215 gene-transcripts) (Achiron et al, Dis Markers 2009). Timepoints of 0, 1, 2, 3 months were used. The study included 9 patients for a total of 36 samples.

1. Repeated-measures ANOVA

ANOVA was run taking into account multiple timepoints from each patient. Variability within patients across timepoints was taken into account in the p value calculation.

2. Immunological cell type enrichment

The ImmGen and DMAP datasets were utilized via the method described (Towfic et al, PLoS One 2013). Briefly, the enrichment method compares in an all-possible-pairwise fashion each cell type against all others. The method then constructs a weighted vector of scores for each cell type. The vector is composed of sets of genes with weights describing the specificity of the genes' expression in a cell type. Finally, the signature from an input dataset is used to compute a score for each cell type, and the score is converted to a p value using a hypergeometric test.

For the human PBMC data, probesets from the rANOVA analysis with nominal p values of <= 0.05 and effect sizes of >= 0.5 in absolute value were used for enrichment. For the mouse splenocyte and human monocyte data, probesets with FDR-adjusted p values <= 0.05 were used for enrichment.

Consensus k-means clustering was used to cluster the gene expression profiles from baseline up to 3 months in the human PBMC dataset. The clustering yielded 5 clusters, 3 of which showed significant cell type enrichments, shown in Table 7.

C. Conclusion

For the foregoing reasons, no ANDA application that references Copaxone® as the RLD should be approved unless and until the conditions set forth above have been satisfied. Because of the extreme complexity of Copaxone®, current analytical technologies can demonstrate, at most, that a proposed generic product is highly similar to Copaxone®, not that it is *identical*, as required by Congress. This means that a generic, if approved via the ANDA pathway without rigorous gene expression studies and without clinical trials in man, could have undetected differences from Copaxone® that make it less safe or effective, including differences that could trigger variable immune responses in patients. The scientific data provided demonstrates that Copaxone® is far more complex than ever imagined.

In summary, the extensive experimental and analytical data gathered by Teva over years of investigation indicates the need to use a combination of high-resolution physicochemical, biological and genome-wide expression methods to detect differences between versions of glatiramer acetate and the branded Copaxone®. Furthermore, in-depth analyses of comparative gene expression profiles in several relevant pre-clinical systems are required in order to allow comprehensive assessment of sameness, given the antigenic nature of Copaxone®. Finally, in order to fully determine the clinical relevance of the recorded differences in physicochemical, biological and genome-wide expression profiling, prospective clinical trials with an adequate follow-up period would ensure the efficacy of the treatment and the safety of MS patients.

III. Environmental Impact

Petitioner claims a categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31(a).

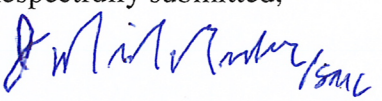
IV. Economic Impact

Petitioner will submit economic information upon request of the Commissioner.

V. Certification

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: June 9, 2014. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organization: my employer, Teva. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,



J. Michael Nicholas, Ph.D.,
Vice President, Global Specialty Medicines

cc: Janet Woodcock, M.D.
Director, Center for Drug Evaluation and Research

Robert Temple, M.D.
Deputy Center Director for Clinical Science
Acting Deputy Director, Office of Drug Evaluation I

Keith Webber, Ph.D.
Acting Director, Office of Pharmaceutical Science

Billy Dunn, M.D.
Acting Director, Division of Neurology Products

Kathleen Uhl, M.D., Acting Director
Office of Generic Drugs

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Appendix 1

Reports from MS Patients complaining about adverse events experienced upon introduction of Probioglat to the Mexican market

Appendix 1A.

Querétaro, Querétaro a 13 de Enero de 2014.

A quien corresponda:
Instituto Mexicano del Seguro Socical:

Por medio de la presente expondré mi caso, soy un paciente pensionado por el seguro social con esclerosis múltiple, he recibido acetato de glatiramer por parte del seguro desde hace 3 años, siendo siempre este el COPAXONE de laboratorio TEVA, pero hace 9 meses comenzaron a darme otro, que de igual forma es acetato de glatiramer, llamado Probioglat de Probiomed, el cual cuando comencé su uso no existieron mayores complicaciones, exceptuando por su aplicación ya que el producto no tiene un aplicador como el copaxone, lo cual me provoco a lo largo de 3 meses de uso, varias "bolitas" en las zonas de aplicación, además de que con el laboratorio Teva se recibe un trato ejemplar, ya que cada mes llaman para saber cómo se encuentra el paciente, como ha llevado su tratamiento, siempre que se solicita envían a una enfermera para apoyar en la aplicación del medicamento, pero lo más importante es que el medicamento cuando lo cambie comencé a sentir problemas después de 3 años de no padecer nada con mi enfermedad, y hace unos días caí nuevamente en el hospital una semana con metilprednisona por vía intravenosa para desinflamación de la medula después de tres años de no tener problemas con COPAXONE, esto aunado a la falta de medicamento que se tuvo en algunas ocasiones.
Por esta razón quisiera solicitar de la manera más atenta que en momento de que me proporcionen acetato de glatiramer como producto activo, se me proporcione exclusivamente el de laboratorio Teva (copaxone), ya que en mi caso particular se hizo notar un cambio y este cambio me llevo al hospital.
Sin más por el momento agradezco la atención prestada a la presente y esperando una respuesta afirmativa por parte de esta institución, envió un cordial saludo.

Atentamente

Carlos Alberto Acosta Barba

Appendix 1B.

From: Juan Verdi

Sent: Monday, February 10, 2014 5:06 PM

To: Augusto Grinspan

Subject: FW: Probiloglat de Probiomed

Attachments: Carta de Copaxone a Seguro.docx

Este caso es interesante por la reacción que se presento

From: Compartiendo Soluciones

Sent: Lunes, 10 de Febrero de 2014 09:47 a.m.

To: Maria Eguia

Subject: RV: Probiloglat de Probiomed

Ma Jo este el el caso que te mencione hace unos minutos

Quedo a tus ordenes

Buen día

De: Yahoo [presmin1@yahoo.com.mx]

Enviado el: lunes, 13 de enero de 2014 02:37 p.m.

Para: Compartiendo Soluciones

Asunto: Probiloglat de Probiomed

Buenas tardes por este medio les hago llegar un caso de problemáticas con el medicamento PROBIOGLAT que me es recetado por el Instituto del Seguro Social, ya que me es recetado a acusa de mi enfermedad que es ESCLEROSIS MÚLTIPLE, y gracias a el cambio de medicamento fui a parar al hospital después de 3 años con dicha enfermedad, les envió adjunto con el caso.

Muchas gracias por la atención prestada a el presente, esperando su pronta respuesta ya que el Seguro Social no me proporciona COPAXONE que es el medicamento que en mis 4 años de enfermedad no me había causado complicaciones.

Solo es para hacer de su conocimiento el caso con el que me encuentro actualmente, este correo se lo tal cual esta a la COFEPRIS si pudieran ayudarme seria genial... Muchas gracias

Atte.

Carlos Alberto Acosta Barba

cel. 045 442 286 65 60

Appendix 1C.

From: Juan Verdi

Sent: Monday, February 10, 2014 5:04 PM

To: Augusto Grinspan

Subject: FW: Reporte de tratamiento. CARTA PACIENTE

Una de las cartas

De: Eduardo Ucan <umdycsa@gmail.com>

Fecha: 14 de febrero de 2013 19:28:53 CST

Para: humberto.juarez@imss.gob.mx

Cco: ug.eduardo.ucan@gmail.com

Asunto: Reporte de tratamiento.

Atención: Dr. Humberto Juárez.

Jefe del Área de Neurología.

U.M.A.E. HOSPITAL DE ESPECIALIDADES

CENTRO MEDICO NACIONAL LA RAZA.

A su atento conocimiento:

Soy Eduardo Ucán Araos, derechohabiente del IMSS, No.

del S.S. 2090-51-0164-6 1M1951OR.

De la UMF 14.

Fecha de nacimiento 18/feb/1952

Con domicilio en: ote. 172 # 287 Col. Moctezuma 2a. sec.

C.P. 15530 Del. Venustiano Carranza en México D.F..

Tel. 55 7121 90.

Padezco Esclerosis múltiple, y desde el 18 de octubre de 2012 he recibido tratamiento con Acetato de Glatiramer, una ampolleta de 20 mg/ 1Ml diaria..

El tratamiento comenzó con un producto llamado COPAXONE de Teva Pharmaceuticals México.

Junto con la primera dosis (28 ampoyetas), recibé asesoría personal en mi domicilio para la aplicación y uso del medicamento, recomendaciones, un paquete conteniendo aplicador y contenedores para almacenaje, transporte y refrigarecián. Una bitácora para el control diario de las aplicaciones, con los teléfonos para preguntar y reportar cualquier irregualaridad.

Recibó en total 3 (tres) dosis de 28 amp. cada una.

Durante este período siempre respondieron al momento (al menos 2 veces) a mis preguntas e inquietudes; y al menos otras 4 (cuatro) , ellos llamaron para saber de mi medicación y otra visita del personal que da seguimiento a los pacientes.

A partir del 08 /diciembre/2013 el COPAXONE fué sustituido por Probioglat de PROBIOMED.

En la aplicación 22 (viernes 8/feb/ 2013 a las 9:15 hrs.) de ésta dotación, experimenté de inmediato los siguientes síntomas:

Escosor (ardor) en dedos y labios.
Presión intensa en el pecho.
Inflamación de labios.
Nauseas.
Debilidad en la voz, (tono bajo, apagado).

Me comunique al teléfono que viene en el instructivo : 55 2581 1937. Ahí me atendió una señorita que transfirió la llamada a otro punto en el cual una grabadora daba el nombre de una persona (mujer) e instruía para que dejarí uno: nombre, teléfono ofreciendo comunicarse posteriormente. Nunca devolvieron la llamada.

Viene otro número al cual también llam00000 36 800 01 :é , en éste me respondió una señorita que también transfirió la llamada a otra señorita que me hizo le diera mi nombre, mi edad, mi teléfono y el motivo de mi llamada; luego que escuchó lo que tenía que decirle, me respondió que ahí no podían ayudarme, que investigara el teléfono del fabricante (PROBIOMED) para solicitar la ayuda.

Los síntomas permanecieron gradualmente disminuyendo hasta el final del día, quedando sólo al día siguiente una molestia general de vaguedad.

Otras anormalidades:

Una ampoyeta rota.

El ajuste de la aguja con la ampoyeta es deficiente, porque en un 20 % de las aplicaciones, el líquido se derrama al momento de ejercer presión con el émbolo. Desde luego que a partir de la primera que sucedió esto, tuve especial cuidado de ejercer la mayor presión posible al colocarla.

El lote que hoy terminé de usar y es el que he descrito es:
4363121206.
Con fecha de caducidad:
05/diciembre/2014

Por su atención a mi reporte, muchas gracias, y espero sean de alguna utilidad mis comentarios.

Atentamente:

Eduardo Ucán Araos.

Appendix 2

Summary of Probioglat adverse event information collected in 2013 via Teva's Patient Support Program: letter of submission to Dr María del Carmen Becerril, head of Pharmacovigilance at Mexico's minister of health (COFEPRIS).

SALUD

COMISIÓN FEDERAL PARA LA PROTECCIÓN CONTRA RIESGOS SANITARIOS

CENTRO INTEGRAL DE SERVICIOS

Comprobante de Trámite

USO EXCLUSIVO COFEPRIS	FORMATO DE ESCRITO LIBRE
143300EL750600	Tipo de Trámite: **EVIDENCIA Y MANEJO DE RIESGOS**
13/03/2014	Homoclave del Trámite:
16:54 hrs.	Subtipo: **OTROS**
	Modalidad: **NO APLICA**

R.F.C. O C.U.R.P.:	**LEM 831109223**
NOMBRE O RAZÓN SOCIAL:	**LEMERY, S.A. DE C.V.**
DOMICILIO:	**MARTIRES DE RIO BLANCO NO. 54**
REPRESENTANTE LEGAL O RESPONSABLE SANITARIO:	**PEDRO PABLO CHAVARRIA JUAREZ**
NÚMERO DE INGRESO DE REFERENCIA:	
ANEXOS:	**OTROS: 8 HOJAS ANEXAS**
REGISTRO SANITARIO:	
NÚM. DE BOLSA DE INF. CONFIDENCIAL:	
NÚM. FOLIO DE BOLSA DE INF. CONFIDENCIAL:	
MODO DE INGRESO Y ENTREGA:	**CENTRO INTEGRAL DE SERVICIOS VENTANILLA**

Para obtener información sobre la disponibilidad de sus trámites usted podrá consultarnos en nuestra página www.cofepris.gob.mx en "Trámites Disponibles" o bien comunicarse al Centro de Atención Telefónica al número: 01 800 033 5050.
Si la resolución de su trámite se encuentra disponible podrá recogerla contra entrega de este comprobante de trámite original en el Centro Integral de Servicios, donde permanecerán disponibles durante 30 días naturales y solo será entregada al representante legal, responsable sanitario o personas autorizadas notificadas ante ésta Comisión Federal previa presentación de identificación oficial.

02 RECIBIDO

Acelata
glatiramer

Appendix 3

Teva's response to the April 29, 2014 "Comment in Opposition to Teva's Sixth Citizen Petition on Copaxone® (Glatiramer Acetate Injection)" submitted by Mylan Pharmaceuticals Inc. (Mylan).

Mylan: "Teva's Sixth Citizen Petition rehashes arguments already rejected by FDA and relies on significantly flawed science largely generated over a year ago …"

Teva's Response: Mylan's comment does not cite or acknowledge the existence of extensive new data, including Teva's peer-reviewed publication in PLOS ONE (Towfic et al, January 8, 2014) and Teva's Type C FDA Meeting material (briefing document and powerpoint slides, February 25, 2014), both of which contain findings that directly refute Mylan's statements. In addition, FDA has not substantively rejected any of the arguments previously made by Teva in its prior Petitions. Without exception, FDA has denied the Petitions "without comment on the specific requirements for approval of any generic version of Copaxone." *See, e.g.,* FDA Petition Response, FDA-2013-P-1641, at 6 (May 2, 2014). Further, the Agency has stated that it "intends to address the issues you have raised, if an when we approve a generic version of Copaxone." *Id.*

Mylan: "none of the products studied are before FDA as a proposed ANDA. Instead, Teva relies on selected foreign glatiramoid products (and even its own failed TV-5010 product) as surrogates for proposed U.S. ANDAs—going so far as to disingenuously refer to the foreign products as 'generics.' "

Teva's Response:

- Teva is committed to characterizing any purported generic glatiramer acetates being marketed to MS patients worldwide, seeking to ensure the safety and efficacious treatment of MS sufferers.

- Teva has publicly offered to characterize any purported generic glatiramer acetate product (including Mylan's) using both gene expression and advanced physicochemical methods.

- In the absence of cooperation from Mylan, Teva has extensively characterized a purported generic glatiramer acetate manufactured by the same company that is manufacturing Mylan's API (Natco Pharma, India).

- The tested Natco product is currently being used to treat MS patients in India. Mylan asserts that Natco is manufacturing a different (and implicitly lower quality) generic glatiramer acetate for use in India than the generic glatiramer acetate they propose for use in the United States. If true, this demonstrates that both companies fail to apply uniform safety standards for MS patients worldwide.

- Moreover, the safety and batch-to-batch manufacturing variability issues identified in Natco's product raise significant concerns about the quality and consistency of the company Mylan has chosen to manufacture their API.

- The USA applicability of investigations employing purported generics, albeit not submitted as ANDAs, relates directly to the clinical relevance of criteria used to define equivalence: by standard physicochemical methodologies and bioassays the purported generics show similarity to Copaxone® and are already in use in clinical practice. It is therefore extremely relevant to define the resolution of characterization methods, including genome-wide expression profiling, and correlate these to treatment response as reported by treating physicians.

- To this end, the gene expression studies raise serious safety concerns, especially related to significant enrichment of pro-inflammatory pathways, which seem to correlate well with reports by healthcare providers from Mexico (Type C FDA Meeting slides 61-62).

- The dramatic differences observed between purported generics (from Natco and other manufacturers) and Copaxone® demonstrate that, despite good faith efforts by experienced manufacturers, current technologies are simply insufficient to ensure that a differently manufactured glatiramoid is the same as Copaxone®.

Mylan: "Teva's analyses suffer from fatal design flaws, including the use of imbalanced sample sizes and a decision not to use pair-wise comparisons between the three sample groups, a focus on only a selected small subset of genes (at most 0.28%) with a significantly different expression when the clinical relevance of those genes is simply unknown, and a failure to verify any study results."

Teva's Response:

- Sample size differences were statistically assessed and reported in Towfic et al: "To ensure the robustness of the result, we randomly selected 11 samples from GA to match the 11 samples from generic, merging technical replicates to eliminate technical variability. We conducted a sensitivity analysis by repeating this process 10 times. Even by this strict method, the number of probes

with greater variability in generic than GA was still significantly higher than the number of probes with greater variability in GA than generic (p,0.00089 by paired t-test, Figure S1B), consistent with the findings above."

- Extensive pair-wise comparisons between sample groups were reported in Towfic et al: "To find differentially expressed probes between generic and GA, we utilized various statistical tests at the probe level and merged the results across the different methods. First, we computed the statistical significance of differential expression between treatments using the Analysis of Variance (ANOVA) method for each probe [21], adjusting for multiple hypothesis testing using the Benjamini-Hochberg False Discovery Rate (FDR) correction [22]. Next, we utilized Linear Models for Microarray (LIMMA) data analysis [23,24] R package, part of the Bioconductor framework [25], to compare generic and GA samples, fitting a linear model that adjusts for fixed effect from medium (Effect=(GA-generic) – (generic-Medium)). The coefficients for the linear model were tested for significance using a modified t-test (taking into account standard deviation) and the p-values for each probe were adjusted using FDR. [22] In parallel, we used Comparative Marker Selection as implemented in GenePattern [26] to directly compare probes between generic and GA. We applied two separate techniques within this framework; a traditional T-test and a Signal-to-Noise Ratio test (SNR). For each of these two tests, we adjusted the nominal p-values via FDR. For all four tests described, we used an adjusted threshold that was less than or equal to 0.05."

- Teva did not choose to "focus on only a selected small subset of genes", rather, the level of gene expression was tested in an unbiased fashion across the entire genome (>45,000 mRNA probesets), without prior hypothesis about the genes for which expression pattern may be altered. Furthermore, stringent statistical tests and the false discovery rate (FDR) correction for multiple hypotheses were imposed a priori across all tests to ensure robustness of results and minimizing of spurious findings.

- A substantial number of genes are differentially expressed between purported generics and GA, using the above described unbiased approach. Towfic et al reports over 700 "*genes that have significantly higher expression in samples activated by GA than generic as determined by the 4 parametric methods (Table S5),*" representing robust cross validation by independent methodologies.

- The clinical relevance of key genes differentially expressed in response to purported generics (including FOXP3 and CD14) is discussed extensively in the Type C FDA meeting (slides 53-63), and in Towfic et al: "there is a preponderance of evidence suggesting that GA upregulates FoxP3+ Tregs more consistently and more effectively than generic. We have shown that the expression of FoxP3 itself, genes downstream of FoxP3, other known Treg markers, and Treg specific genes are all

enriched from activation by GA relative to generic. This dramatic difference in biological impact on Tregs is certainly of note to physicians and regulators. It is well established that FoxP3+ Tregs induce beneficial tolerance in MS patients by suppressing harmful myelin reactive T cells, [39] so the more variable and reduced Treg induction raises questions about the potential efficacy of generic especially given recent findings demonstrating Copaxone®'s impact on Tregs [36] and linking Tregs to clinical response in MS patients [40].

These methods also identified specific genes and immune cell types that are upregulated significantly more by generic than by GA. In this case, generic had a significantly higher impact on cells of the myeloid lineage such as monocytes and macrophages than GA did. Genes with significantly higher expression in generic than in GA include key monocyte markers such as CD14, enrich to macrophage and monocyte cell types, and are enriched in related pathways such as TLR signaling. The stronger upregulation of monocyte-specific genes warrants further investigation by physi- cians and regulators, especially given that monocytes are "prominent contributors" to neuroinflammation in MS [41] and given recent reports that one of GA's mechanisms of action involves its impact on monocytes [37], [12]."

- Verification and follow up studies, including RT-PCR analyses, where conducted and reported in the Type C FDA meeting (e.g. slide 51): "Data is based on 6 biological samples with 15 technical replicates and normalization to the house keeping gene, GAPDH". Additional data is being summarized for publication in the peer-reviewed literature.

Mylan: "If Teva's abusive submissions either prevent or delay the approval of an ANDA referencing Copaxone® at the earliest possible date, Teva will receive an unfair windfall, patients will be deprived of an affordable therapy, and the U.S. healthcare system will incur millions of dollars in unnecessary costs."

Teva's Response: Teva's top priority is to ensure that patient safety is not compromised, which cannot be guaranteed by current characterization methods, which do not ensure that purported generic versions contain the same active ingredient as, are bioequivalent to, and have the same low risk of immunogenicity as Copaxone®.

Mylan: "Similarly, Teva continues to cite its own failed TV-5010 product as a surrogate for U.S. ANDAs. In so doing, Teva attempts to raise the specter that any generic version of Copaxone® will be toxic. However, based on the apparent characteristics of TV-5010, it seems a particularly problematic choice as a surrogate for a generic equivalent to Copaxone®."

Teva's Response:

While Teva represents in its citizens' petition that TV-5010 was a developmental glatiramoid (intended as an NCE), the experience with this compound is critical because it demonstrates three key points:

- Gene expression studies can identify predictive signatures of specific toxicity and tolerability phenotypes. This demonstrates the potential clinical relevance of findings in the purported generics experiments, raising considerable concerns for compromised patient safety.

- The antigenic nature of polypeptides comprising glatiramoids is unique. Any alteration, even if only in molecular weight but NO OTHER manufacturing element, can result in serious toxicity as observed with TV-5010 and described in the publically available minutes from the FDA Type C meeting held 25 February 2014.

- Short-term animal studies and pre-clinical characterization of the glatiramoid TV-5010 did not identify the serious long-term toxicity and fatalities seen in two different species. It is therefore cannot be assumed that differently manufactured glatiramoids will be safe unless tested in full clinical trials with appropriate endpoints.

Mylan: " … the differences in variability among Copaxone® batches and among GA-Natco batches are modest."

Teva's Response:

- The substantially higher batch-to-batch variability observed in the purported generic Natco product relative to Copaxone® was cross validated by use of three different and independent methods in Towfic et al and yet a fourth independent method in the Type C FDA meeting (slide 91). Moreover, the high variability seen across 5 manufacturing batches of Natco's purported generic would only increase with the addition of more batches.

Mylan: "In sum, Teva is simply wrong: FDA is not precluded from finding active ingredient sameness because Copaxone® is a synthetic peptide drug product or because ANDAs that reference Copaxone® are seeking approval for synthetic generic versions of that drug. FDA's Premarin® decision does not dictate a contrary result and, in fact, following the Premarin® decision FDA has approved several ANDAs for synthetic generic versions of synthetic drug products"

Teva's Response: Proclamations need to be supported by data. Teva has provided extensive peer-reviewed data to support its statements, and is committed to generate additional validated evidence.

Moreover, Teva never asserted that FDA is precluded from approving synthetic versions of peptide drug products. Indeed, Teva specifically indicated that some peptide drug products adequately characterized because of their small size and relative lack of tertiary structure. Within the class of synthetic peptide drugs, Copaxone® is unique in that it is composed of millions of different polypeptides with a size and structure similar to proteins, lacks a PK profile as well as a validated PD biomarker and demonstrates NBCD properties, as described in numerous peer-reviewed publications. Under these circumstances, as discussed in detail in Teva's prior Petitions, and because Copaxone®'s "starting material" is proprietary, FDA is precluded from relying upon the "same starting material" as a surrogate marker for sameness. Because this is a required element of any overlapping criteria approach, the fact that Copaxone® is synthetic and is manufactured from a protected starting material precludes the approval of generic versions based upon an overlapping criteria approach.

Supplementary Table 1:

Mouse splenocyte study: probesets significantly modulated by GA relative to Natco (Towfic et al, Table S5).

TABLE S5													
			Comparative Marker Selection								Significant in Parametric Tests		
			T-test		SNR		LIMMA		ANOVA			Wilcoxon Rank Sum	
Probe	Gene	Fold Change	Nom. P.	Adj. P.	Nom. P.	Adj. P.	Nom. P.	Adj. P.	Nom. P.	Adj. P.	1-yes,0-no	Nom. P.	Adj. P.
ILMN_2685712	IFNG	1.41	0.0002995	0.01489206	0.0002995	0.01335371	2.36E-07	0.0000718	4.01E-07	0.000139	1	2.06483E-05	0.00430994
ILMN_2595857	ANKRD37	1.36	0.0002995	0.01489206	0.0002995	0.01335371	5.82E-12	1.69E-08	1.23E-08	0.0000119	1	6.03547E-07	0.00057333
ILMN_2791459	IFNG	1.33	0.0002995	0.01489206	0.0002995	0.01335371	0.00000199	0.00037564	0.00000642	0.00108	1	0.000197175	0.01547711
ILMN_2675232	KLK8	1.284884601	0.0002995	0.01489206	0.0002995	0.01335371	7.43E-19	3.46E-14	5.6E-14	2.61E-09	1	7.95833E-09	0.00012222
ILMN_1220788	GM590	1.284311292	0.0002995	0.01489206	0.0002995	0.01335371	3.92E-10	0.00000057	4.06E-09	0.00000573	1	4.9657E-07	0.00052531
ILMN_1253828	CD247	1.280944226	0.0002995	0.01489206	0.0002995	0.01335371	7.18E-09	0.00000514	1.89E-07	0.0000836	1	1.53585E-05	0.00359242
ILMN_2856926	GPR114	1.275591039	0.0002995	0.01489206	0.0002995	0.01335371	3.75E-15	5.82E-11	5.66E-11	0.000000293	1	5.89499E-08	0.00024945
ILMN_1218037	TMIE	1.25825101	0.0002995	0.01489206	0.0002995	0.01335371	1.6E-10	2.67E-07	8.95E-09	0.0000105	1	1.80477E-06	0.001091
ILMN_2664929	CD8B1	1.257683544	0.0002995	0.01489206	0.0002995	0.01335371	6.15E-13	2.6E-09	8E-11	0.000000367	1	1.49655E-07	0.00034541
ILMN_1240428	SATB1	1.253362369	0.0002995	0.01489206	0.0002995	0.01335371	3.36E-10	5.04E-07	3.35E-08	0.0000244	1	2.88347E-07	0.00041943
ILMN_2741169	CD8B1	1.24933849	0.0002995	0.01489206	0.0002995	0.01335371	2.32E-15	5.4E-11	3.06E-12	4.75E-08	1	1.57497E-07	0.00034541
ILMN_1250001	4930583H14RIK	1.24042799	0.00094262	0.02607154	0.0006399	0.01941092	0.00000259	0.00046493	0.000033	0.003242217	1	0.000130304	0.01220373
ILMN_2611022	BCL11B	1.239019043	0.0002995	0.01489206	0.0002995	0.01335371	7.52E-10	9.15E-07	0.00000014	0.0000707	1	1.5356E-05	0.00359242
ILMN_2707941	GPR83	1.238234714	0.0002995	0.01489206	0.0002995	0.01335371	9.31E-14	8.67E-10	2.22E-12	4.75E-08	1	1.65715E-07	0.00034541
ILMN_2769772	PIK3IP1	1.235639618	0.0002995	0.01489206	0.0002995	0.01335371	8.08E-12	2.21E-08	2.26E-09	0.00000363	1	4.9657E-07	0.00052531
ILMN_2775055	LOC669166	1.234427524	0.0002995	0.01489206	0.0002995	0.01335371	3.92E-12	1.4E-08	2.69E-09	0.00000405	1	4.7283E-07	0.00052531
ILMN_3128992	CD27	1.229968408	0.0002995	0.01489206	0.0002995	0.01335371	5.34E-13	2.48E-09	8.67E-11	0.000000367	1	1.10038E-07	0.00029962
ILMN_2416460	TRBV8_AE000663_	1.227075821	0.0002995	0.01489206	0.0002995	0.01335371	5.05E-12	1.57E-08	2.14E-09	0.00000357	1	2.49646E-06	0.00133566
ILMN_2670150	OAS2	1.223676484	0.0002995	0.01489206	0.0002995	0.01335371	1.69E-08	0.0000104	2.75E-07	0.000109783	1	1.80477E-06	0.001091
ILMN_2454209	TRBV6_AE000663_	1.223323464	0.0002995	0.01489206	0.0002995	0.01335371	4.23E-09	0.00000323	0.00000012	0.0000626	1	0.000103509	0.01061242
ILMN_2960700	PRF1	1.220037267	0.0002995	0.01489206	0.0002995	0.01335371	0.00000023	0.0000712	0.00000418	0.000771264	1	3.99889E-05	0.00618393
ILMN_1229318	PDK1	1.219922378	0.0002995	0.01489206	0.0002995	0.01335371	1.26E-09	0.00000128	5.7E-08	0.0000353	1	1.98091E-06	0.00115257
ILMN_1233589	CD27	1.219317837	0.0002995	0.01489206	0.0002995	0.01335371	3.67E-13	1.9E-09	1.77E-11	0.000000121	1	2.95621E-08	0.00022934
ILMN_2678521	GPR146	1.215770831	0.0002995	0.01489206	0.0002995	0.01335371	1.33E-13	8.87E-10	3.83E-11	0.000000223	1	7.26855E-08	0.00026025
ILMN_1256701	2900016B01RIK	1.215770789	0.0002995	0.01489206	0.0002995	0.01335371	2.75E-08	0.0000147	4.48E-07	0.000148861	1	2.54447E-05	0.00475651
ILMN_1215167	DDX5	1.214758445	0.0006399	0.0211535	0.0006399	0.01941092	0.00010165	0.00670197	0.0000543	0.004539402	1	7.0054E-05	0.00846962
ILMN_3145331	TMSB10	1.209579271	0.0002995	0.01489206	0.0002995	0.01335371	4.98E-12	1.57E-08	1.59E-10	0.000000461	1	2.13433E-07	0.00036795
ILMN_1252200	A830055I09RIK	1.206497974	0.0002995	0.01489206	0.0002995	0.01335371	0.00000761	0.0010354	0.0000334	0.003276709	1	5.74504E-05	0.00761864
ILMN_2819380	BC030476	1.206275831	0.0002995	0.01489206	0.0002995	0.01335371	0.000036	0.00314503	0.00012566	0.008308344	1	0.000197175	0.01547711
ILMN_2932359	TPI1	1.204626968	0.0002995	0.01489206	0.0002995	0.01335371	5.08E-08	0.0000227	0.0000011	0.000288061	1	1.53585E-05	0.00359242
ILMN_2837493	EG634650	1.204245484	0.0002995	0.01489206	0.0002995	0.01335371	5.69E-08	0.0000248	5.02E-08	0.0000324	1	4.9657E-07	0.00052531
ILMN_1230137	TPI1	1.204175926	0.0002995	0.01489206	0.0002995	0.01335371	2.06E-08	0.0000124	0.00000121	0.000298774	1	2.88127E-05	0.00509941
ILMN_2944666	IFIT3	1.202746675	0.0002995	0.01489206	0.0002995	0.01335371	5.52E-08	0.0000242	2.84E-08	0.0000217	1	2.74304E-07	0.00041187
ILMN_1217855	NKG7	1.202473931	0.0006399	0.0211535	0.0006399	0.01941092	2.84E-08	0.0000149	5.31E-07	0.000169129	1	0.000264806	0.01861919
ILMN_2699898	ITGAE	1.201910561	0.0002995	0.01489206	0.0002995	0.01335371	1.42E-11	3.32E-08	1.38E-10	0.000000429	1	1.04521E-07	0.00029962
ILMN_2516221	TCRB-V8.2	1.20121668	0.0002995	0.01489206	0.0002995	0.01335371	1.11E-08	0.00000752	4.35E-07	0.000147963	1	1.13766E-05	0.00307877
ILMN_2652867	TRAT1	1.199470243	0.0002995	0.01489206	0.0002995	0.01335371	6.33E-10	8.19E-07	3.26E-08	0.0000241	1	4.12145E-06	0.00171287
ILMN_1229197	OTTMUSG0000001	1.198389483	0.0002995	0.01489206	0.0002995	0.01335371	4.13E-08	0.00002	1.88E-08	0.0000159	1	9.77116E-07	0.00079793
ILMN_2618148	C330008K14RIK	1.196159524	0.0002995	0.01489206	0.0002995	0.01335371	2.81E-11	5.95E-08	1.46E-08	0.000013	1	1.18196E-06	0.00088737
ILMN_1214841	IL24	1.195664917	0.00094262	0.02607154	0.00094262	0.02430167	0.0000373	0.00322909	0.00014082	0.009031912	1	0.002173782	0.0607706

ILMN_1257496	LOC665446	1.195420235	0.0002995	0.01489206	0.0002995	0.01335371	8.57E-08	0.0000344	0.00000185	0.000412402	1	1.47177E-05	0.00353126
ILMN_2421246	TCRB-V8.3	1.195307771	0.0002995	0.01489206	0.0002995	0.01335371	1.42E-09	0.00000136	4.63E-08	0.0000308	1	5.89742E-06	0.0021116
ILMN_2729252	5830431A10RIK	1.195292385	0.0002995	0.01489206	0.0002995	0.01335371	1.38E-09	0.00000136	2.06E-08	0.0000171	1	1.2393E-06	0.00090134
ILMN_2484932	C030002B11RIK	1.193361778	0.0002995	0.01489206	0.0002995	0.01335371	6.33E-10	8.19E-07	5.47E-08	0.0000344	1	8.06586E-07	0.00070845
ILMN_1221819	FCGRT	1.193070246	0.0002995	0.01489206	0.0002995	0.01335371	7.12E-09	0.00000514	2.33E-08	0.0000187	1	9.56517E-06	0.00274856
ILMN_2981167	IFIT2	1.192834198	0.0002995	0.01489206	0.0002995	0.01335371	2.31E-08	0.000013	1.07E-08	0.0000115	1	3.88359E-07	0.00048857
ILMN_2585233	SELPL	1.192768508	0.0002995	0.01489206	0.0002995	0.01335371	8.22E-10	9.34E-07	8.63E-08	0.0000485	1	1.41024E-05	0.00347315
ILMN_2697415	CD3D	1.191227881	0.0002995	0.01489206	0.0002995	0.01335371	5.84E-10	7.99E-07	3.71E-08	0.0000262	1	5.64085E-06	0.00208385
ILMN_1230345	B830007D08RIK	1.191119956	0.0002995	0.01489206	0.0002995	0.01335371	3.22E-09	0.00000253	1.09E-08	0.0000115	1	1.57497E-07	0.00034541
ILMN_2811263	ZXDA	1.190267135	0.0002995	0.01489206	0.0006399	0.01941092	0.0000175	0.00184283	0.00015367	0.009469751	1	0.000176289	0.01444673
ILMN_2560567	A630006E02RIK	1.189860092	0.0002995	0.01489206	0.0002995	0.01335371	0.0000009	0.00020543	0.0000211	0.002464033	1	9.21443E-05	0.00995203
ILMN_2820893	SELPLG	1.188849449	0.0002995	0.01489206	0.0002995	0.01335371	1.27E-13	8.87E-10	8.13E-12	7.57E-08	1	5.59305E-08	0.00024945
ILMN_1246609	RASGRP1	1.18775349	0.0002995	0.01489206	0.0002995	0.01335371	3.02E-11	6.12E-08	2.46E-09	0.00000382	1	3.34766E-07	0.00044521
ILMN_2660551	LAT	1.187218377	0.0002995	0.01489206	0.0002995	0.01335371	9.43E-07	0.00021216	0.00000642	0.001075031	1	0.000130304	0.01220373
ILMN_2507761	7530404M11RIK	1.186381811	0.0002995	0.01489206	0.0002995	0.01335371	0.0000307	0.00278714	0.0000826	0.006091257	1	9.21504E-05	0.00995203
ILMN_2753697	CD2	1.186334291	0.0002995	0.01489206	0.0002995	0.01335371	2.97E-13	1.73E-09	1.04E-10	0.000000395	1	1.92936E-07	0.00034541
ILMN_2601453	A130092J06RIK	1.186313516	0.0002995	0.01489206	0.0002995	0.01335371	3.23E-11	6.26E-08	9.08E-10	0.00000192	1	9.77016E-07	0.00079793
ILMN_1234565	P4HA1	1.18626686	0.0002995	0.01489206	0.0002995	0.01335371	1.07E-07	0.0000412	7.49E-07	0.000219513	1	8.39227E-06	0.00252023
ILMN_2459899	ADAMTSL4	1.185956519	0.0002995	0.01489206	0.0002995	0.01335371	2.09E-09	0.00000174	2.06E-07	0.0000903	1	3.93982E-06	0.00166715
ILMN_2761720	LOC100041103	1.185737904	0.0002995	0.01489206	0.0002995	0.01335371	1.19E-09	0.00000123	3.43E-08	0.0000245	1	9.77016E-07	0.00079793
ILMN_1213954	SGK1	1.185317215	0.0002995	0.01489206	0.0002995	0.01335371	1.06E-07	0.000041	3.55E-07	0.000132883	1	1.49642E-06	0.00102442
ILMN_2632971	B3GALT4	1.185249067	0.0002995	0.01489206	0.0002995	0.01335371	1.78E-09	0.00000151	2.34E-10	0.000000605	1	6.36427E-09	0.00012222
ILMN_2860649	GBP6	1.184770963	0.0002995	0.01489206	0.0002995	0.01335371	0.00000014	0.0000492	1.01E-07	0.0000545	1	1.72245E-06	0.00108344
ILMN_2722784	CD3G	1.184582149	0.0002995	0.01489206	0.0002995	0.01335371	4.91E-08	0.0000224	0.00000016	0.0000754	1	2.06467E-05	0.00430994
ILMN_2667829	PRKCQ	1.183849443	0.0002995	0.01489206	0.0002995	0.01335371	2.77E-11	5.95E-08	1.89E-10	0.000000518	1	8.49731E-08	0.00028252
ILMN_1235499	PROS1	1.183674675	0.0002995	0.01489206	0.0002995	0.01335371	4.45E-07	0.00012175	0.00000119	0.00029799	1	2.24533E-05	0.00440984
ILMN_2694955	IGFBP4	1.183278575	0.0002995	0.01489206	0.0002995	0.01335371	0.00000158	0.00031636	0.00000706	0.001150107	1	9.95836E-05	0.01046347
ILMN_2491445	LOC639001	1.183039504	0.0006399	0.0211535	0.0002995	0.01335371	2.23E-08	0.0000126	4.29E-07	0.000146987	1	4.70154E-05	0.00688184
ILMN_2661185	SCML4	1.18284704	0.0002995	0.01489206	0.0002995	0.01335371	0.00000016	0.0000542	0.0000016	0.000369569	1	1.81978E-05	0.00399552
ILMN_2454823	6720418B01RIK	1.182721445	0.0002995	0.01489206	0.0002995	0.01335371	0.0000166	0.00178634	0.00013436	0.00874694	1	0.00057968	0.02968357
ILMN_2947526	ECM1	1.181777956	0.0002995	0.01489206	0.0002995	0.01335371	0.00000016	0.0000542	7.57E-07	0.000219513	1	7.35697E-06	0.00232956
ILMN_2705407	PABPC1	1.181328619	0.00094262	0.02607154	0.0006399	0.01941092	0.00011396	0.00731485	0.00024603	0.012809759	1	0.000329201	0.02128238
ILMN_1227570	LOC386545	1.180241912	0.0006399	0.0211535	0.0002995	0.01335371	1.36E-07	0.0000491	0.00000102	0.000272691	1	5.30373E-05	0.00748099
ILMN_2475156	XIST	1.179666178	0.0006399	0.0211535	0.0006399	0.01941092	0.00036367	0.01638681	0.00063489	0.023714186	1	0.001104095	0.04229821
ILMN_1214650	SCL0002368.1_75	1.179443236	0.0002995	0.01489206	0.0002995	0.01335371	0.0000372	0.00322909	0.0000222	0.00254822	1	3.68613E-05	0.00599924
ILMN_2606825	CMAH	1.17926401	0.0002995	0.01489206	0.0002995	0.01335371	1.13E-07	0.0000431	3.18E-07	0.000121491	1	7.35697E-06	0.00232956
ILMN_1224032	SKAP1	1.178850818	0.0002995	0.01489206	0.0002995	0.01335371	1.24E-08	0.00000822	6.12E-08	0.0000375	1	3.76554E-06	0.00162291
ILMN_2436183	BCL11B	1.178588337	0.0002995	0.01489206	0.0002995	0.01335371	8.65E-08	0.0000344	0.00000254	0.000523539	1	4.7012E-05	0.00688184
ILMN_2419490	TNFRSF18	1.178043424	0.0002995	0.01489206	0.0002995	0.01335371	7.56E-11	1.35E-07	1.53E-08	0.0000132	1	1.56849E-06	0.00104298
ILMN_2432110	LOC100046855	1.176564584	0.0002995	0.01489206	0.0002995	0.01335371	1.32E-07	0.0000482	9.52E-08	0.0000521	1	1.12718E-06	0.00087445
ILMN_2443624	BCL11B	1.17644894	0.0002995	0.01489206	0.0002995	0.01335371	2.53E-07	0.0000755	0.00000244	0.000512485	1	2.24533E-05	0.00440984
ILMN_1217913	D230007K08RIK	1.176197032	0.0002995	0.01489206	0.0002995	0.01335371	2.34E-08	0.000013	8.68E-08	0.0000485	1	1.02476E-06	0.0008224
ILMN_1215649	C230075M21RIK	1.176099557	0.0002995	0.01489206	0.0002995	0.01335371	0.0000672	0.00493359	0.00041344	0.017763501	1	0.000393771	0.02371136
ILMN_1217629	ITGAE	1.175144353	0.0002995	0.01489206	0.0002995	0.01335371	2.19E-08	0.0000126	1.49E-08	0.0000131	1	4.51028E-06	0.00180983
ILMN_1215862	CXCL9	1.174363745	0.00176049	0.0385938	0.00122569	0.02881591	0.01957651	0.17739607	0.00069086	0.02516235	0	0.001301571	0.04617913
ILMN_2721399	CTSW	1.172718248	0.0002995	0.01489206	0.0002995	0.01335371	2.77E-10	4.45E-07	4.69E-09	0.00000642	1	1.8046E-06	0.001091
ILMN_1248340	LSG1	1.172636468	0.0002995	0.01489206	0.0002995	0.01335371	0.00000275	0.00048633	0.0000158	0.00199766	1	2.65234E-05	0.00480383

ILMN_2618176	SOCS3	1.171028633	0.0002995	0.01489206	0.0002995	0.01335371	5.43E-10	7.65E-07	2.48E-08	0.0000192	1	7.35697E-06	0.00232956
ILMN_1218717	LOC385615	1.170940971	0.0002995	0.01489206	0.0002995	0.01335371	0.00000442	0.00070872	0.0000267	0.002856495	1	7.57938E-05	0.00879794
ILMN_1247893	CGEF2-PENDING	1.169922593	0.0002995	0.01489206	0.0002995	0.01335371	0.00000467	0.00072982	0.0000243	0.002709534	1	0.000120719	0.01149104
ILMN_1224473	LOC380797	1.16992167	0.00122569	0.03054155	0.00094262	0.02430167	0.00015376	0.00895396	0.00147216	0.0392018	1	0.00305523	0.07341857
ILMN_2419494	TNFRSF18	1.169716279	0.0002995	0.01489206	0.0002995	0.01335371	7.66E-10	9.15E-07	4.99E-08	0.0000324	1	5.39498E-06	0.00202516
ILMN_2612125	ARHGEF18	1.169661163	0.0002995	0.01489206	0.0002995	0.01335371	4.41E-08	0.0000212	0.00000152	0.000360463	1	9.15833E-06	0.00268109
ILMN_2606162	PDLIM4	1.169633574	0.0006399	0.0211535	0.0002995	0.01335371	4.78E-07	0.00012706	0.00000832	0.001279253	1	0.000600122	0.03046224
ILMN_1217406	1110013L07RIK	1.169153834	0.0002995	0.01489206	0.0002995	0.01335371	4.77E-08	0.0000223	2.86E-07	0.000110081	1	1.13766E-05	0.00307877
ILMN_2568571	C130079K02RIK	1.168909165	0.0002995	0.01489206	0.0002995	0.01335371	5.37E-07	0.00013971	0.0000201	0.002389566	1	6.22097E-05	0.00789013
ILMN_2818964	DUSP10	1.168854568	0.0002995	0.01489206	0.0002995	0.01335371	0.0000386	0.00328743	0.000041	0.003797436	1	3.39668E-05	0.00570777
ILMN_2431390	TCRB-V8.2	1.167218786	0.0006399	0.0211535	0.0002995	0.01335371	1.7E-09	0.00000149	7.75E-08	0.0000451	1	1.23973E-05	0.00322459
ILMN_2456911	TRBV31_X03277_T	1.166841194	0.0006399	0.0211535	0.0002995	0.01335371	0.00000163	0.00032459	0.0000123	0.001649893	1	0.000540727	0.02850419
ILMN_2981169	IFIT2	1.165766787	0.0002995	0.01489206	0.0002995	0.01335371	0.0000117	0.00139985	0.00000211	0.00045645	1	3.43889E-06	0.00156931
ILMN_1249366	LOC100046608	1.165718568	0.0002995	0.01489206	0.0002995	0.01335371	1.59E-09	0.00000145	1.55E-07	0.0000735	1	5.64035E-06	0.00208385
ILMN_1246194	LOC667370	1.165517165	0.0002995	0.01489206	0.0002995	0.01335371	0.0008987	0.02917128	0.00023641	0.012496999	1	0.00022037	0.01646479
ILMN_1236507	5830496L11RIK	1.164879502	0.0002995	0.01489206	0.0002995	0.01335371	0.0000665	0.00488934	0.00043189	0.018308965	1	0.000486846	0.02669165
ILMN_1254692	MS4A6B	1.164318447	0.0002995	0.01489206	0.0002995	0.01335371	0.00000049	0.00012954	8.08E-07	0.000227616	1	3.59866E-06	0.00158025
ILMN_3156208	GPR146	1.164011442	0.0002995	0.01489206	0.0002995	0.01335371	2.38E-08	0.000013	3.86E-07	0.00013797	1	6.44447E-06	0.00218957
ILMN_2734391	RAMP1	1.16383138	0.0002995	0.01489206	0.0002995	0.01335371	5.98E-09	0.00000442	2.14E-09	0.00000357	1	3.18544E-07	0.00044521
ILMN_1224091	XIST	1.16230787	0.0006399	0.0211535	0.00094262	0.02430167	0.00084048	0.02804442	0.00095208	0.030395331	1	0.001531279	0.05016159
ILMN_2456216	5330403D14RIK	1.161809103	0.00094262	0.02607154	0.00094262	0.02430167	0.0000367	0.00319787	0.00031494	0.015019787	1	0.000903743	0.03800048
ILMN_2627441	PELI1	1.161752176	0.0002995	0.01489206	0.0002995	0.01335371	0.00000119	0.00025415	0.00000113	0.000290416	1	4.31186E-06	0.00177614
ILMN_2891245	RHBDL2	1.161573842	0.0020184	0.04200694	0.0020184	0.03953445	0.00050184	0.02040365	0.00120654	0.035013094	1	0.001977573	0.05767797
ILMN_1232804	LOC276837	1.161420855	0.0002995	0.01489206	0.0002995	0.01335371	3.19E-07	0.0000928	0.000001	0.000269028	1	6.47271E-05	0.00803428
ILMN_1232537	ARL4C	1.160980448	0.0002995	0.01489206	0.0002995	0.01335371	4.13E-07	0.000115	0.00000371	0.000722503	1	7.28705E-05	0.00865281
ILMN_2444432	TRBV1_AE000663	1.160799824	0.0002995	0.01489206	0.0002995	0.01335371	0.00000104	0.00022691	0.00000112	0.000290018	1	7.57938E-05	0.00879794
ILMN_2756046	FFAR2	1.160027707	0.0002995	0.01489206	0.0002995	0.01335371	0.0000389	0.00330056	1.33E-07	0.000068	1	2.99936E-06	0.00146959
ILMN_1214163	B230380D07RIK	1.159421403	0.0002995	0.01489206	0.0002995	0.01335371	6.66E-08	0.0000279	4.61E-07	0.000152045	1	4.16456E-05	0.00639762
ILMN_2613832	MGST2	1.159082249	0.0002995	0.01489206	0.0002995	0.01335371	0.00000018	0.0000594	1.27E-08	0.0000119	1	1.49656E-06	0.00102442
ILMN_2506039	A130090K04RIK	1.158817015	0.0002995	0.01489206	0.0002995	0.01335371	6.61E-07	0.0001602	4.04E-07	0.00013924	1	7.03988E-06	0.00230764
ILMN_1219179	A830081L15RIK	1.158794735	0.0002995	0.01489206	0.0002995	0.01335371	0.00000165	0.00032655	0.00000379	0.000732759	1	8.39227E-06	0.00252023
ILMN_1248898	A830092P18RIK	1.158658732	0.0002995	0.01489206	0.0002995	0.01335371	0.00000523	0.00078323	0.0000278	0.002931426	1	9.5799E-05	0.01018072
ILMN_2651575	IFNGR1	1.158581155	0.0002995	0.01489206	0.0002995	0.01335371	5.63E-07	0.00014332	0.00000707	0.001150107	1	1.1878E-05	0.00314139
ILMN_2708580	INADL	1.158423303	0.0002995	0.01489206	0.0002995	0.01335371	1.33E-07	0.0000482	2.41E-07	0.000101903	1	3.76554E-06	0.00162291
ILMN_1236256	ARHGEF1	1.158058706	0.0002995	0.01489206	0.0006399	0.01941092	0.00012116	0.00760514	0.00023881	0.012588785	1	0.00022037	0.01646479
ILMN_2525855	FUS	1.157139415	0.0002995	0.01489206	0.0002995	0.01335371	0.0000124	0.00144807	0.0000814	0.006023296	1	9.5799E-05	0.01018072
ILMN_2526938	LOC623121	1.157084959	0.0002995	0.01489206	0.0002995	0.01335371	0.0000881	0.00606307	0.0001654	0.009948464	1	0.000393771	0.02371136
ILMN_1213664	LOC665425	1.156699853	0.00094262	0.02607154	0.0006399	0.01941092	0.00000457	0.0007204	0.0000219	0.002525607	1	0.000157497	0.01350097
ILMN_1255743	IL6RA	1.1564233	0.0002995	0.01489206	0.0002995	0.01335371	0.0000121	0.00143247	0.0000346	0.003367292	1	0.00011618	0.0112429
ILMN_2646625	JUN	1.155896052	0.0002995	0.01489206	0.0002995	0.01335371	4.75E-08	0.0000223	4.3E-08	0.0000294	1	8.0667E-07	0.00070845
ILMN_2843019	KLHDC1	1.155520822	0.0002995	0.01489206	0.0002995	0.01335371	5.72E-07	0.00014393	0.00000446	0.000810182	1	3.00244E-05	0.00527375
ILMN_3047389	GBP2	1.155409559	0.00397039	0.064249	0.00467484	0.06877491	0.00439071	0.07547063	0.00354418	0.067235737	0	0.003774648	0.08295494
ILMN_1257639	0610009J05RIK	1.155036694	0.0002995	0.01489206	0.0002995	0.01335371	0.0000254	0.00245781	0.00014036	0.009023792	1	0.000157487	0.01350097
ILMN_1239770	PELI1	1.154754524	0.0002995	0.01489206	0.0002995	0.01335371	2.15E-08	0.0000125	6.23E-08	0.0000377	1	1.56849E-06	0.00104298
ILMN_2669841	6330581N18RIK	1.153993411	0.0002995	0.01489206	0.0002995	0.01335371	0.00000028	0.0000823	1.21E-07	0.0000627	1	1.29931E-06	0.00093044
ILMN_2797061	ACTN2	1.153924476	0.0002995	0.01489206	0.0002995	0.01335371	3.85E-08	0.0000189	1.24E-08	0.0000119	1	1.18196E-06	0.00088737
ILMN_2784580	CD3E	1.153886402	0.00094262	0.02607154	0.0002995	0.01335371	0.00000294	0.00051612	0.0000297	0.003067006	1	0.000763113	0.03482416

ILMN_3006219	FYB	1.153762655	0.0002995	0.01489206	0.0002995	0.01335371	0.0000042	0.0006766	0.0000232	0.002627969	1	0.000157497	0.01350097
ILMN_2467190	BAMBI-PS1	1.15354344	0.0002995	0.01489206	0.0002995	0.01335371	0.00000128	0.00026647	0.0000012	0.00029799	1	2.76434E-05	0.00493033
ILMN_2536349	LOC386513	1.153082558	0.0002995	0.01489206	0.0002995	0.01335371	6.12E-08	0.0000262	4.94E-07	0.00016183	1	4.16456E-05	0.00639762
ILMN_2432550	TRIB2	1.15299348	0.0002995	0.01489206	0.0002995	0.01335371	2.08E-07	0.0000667	3.94E-07	0.00013797	1	6.16514E-06	0.0021257
ILMN_2844996	ACTN1	1.152882536	0.0002995	0.01489206	0.0002995	0.01335371	0.00000474	0.0007333	0.0000112	0.001548243	1	0.000140602	0.01273272
ILMN_1247281	5830468F06RIK	1.15264746	0.0002995	0.01489206	0.0002995	0.01335371	3.03E-07	0.0000888	7.59E-07	0.000219513	1	2.73684E-06	0.00139991
ILMN_1227814	SRR	1.1524679	0.00444101	0.0691859	0.00373333	0.05925673	0.00032551	0.01515171	0.00191731	0.04584872	0	0.004782836	0.09409752
ILMN_1249021	BCL2	1.152415672	0.0002995	0.01489206	0.0002995	0.01335371	2.39E-08	0.000013	2.71E-07	0.000109783	1	7.35697E-06	0.00232956
ILMN_2427592	LOC546630	1.152263699	0.0002995	0.01489206	0.0002995	0.01335371	3.87E-08	0.0000189	7.4E-08	0.0000436	1	8.87963E-07	0.00076541
ILMN_1259075	NME7	1.152030836	0.0002995	0.01489206	0.0002995	0.01335371	6.14E-08	0.0000262	2.53E-07	0.000106116	1	3.43889E-06	0.00156931
ILMN_1343049	control_ILMN_134	1.151797691	0.0006399	0.0211535	0.0006399	0.01941092	0.0000486	0.00386324	0.0000962	0.006777584	1	0.000111795	0.01097902
ILMN_3026397	CHKA	1.1512093	0.00373333	0.06184411	0.00397039	0.06196763	0.0007963	0.02730155	0.00350197	0.066778429	0	0.005373402	0.10008988
ILMN_2631610	TMEM71	1.15055696	0.0002995	0.01489206	0.0002995	0.01335371	0.00000196	0.00037186	7.31E-07	0.000218104	1	2.99936E-06	0.00146959
ILMN_1227434	ITGB7	1.150210635	0.0006399	0.0211535	0.0002995	0.01335371	0.00000383	0.00063236	0.00000744	0.001193798	1	7.57886E-05	0.00879794
ILMN_1232600	RNF125	1.150131069	0.0002995	0.01489206	0.0002995	0.01335371	7.88E-08	0.0000325	5.26E-07	0.000168884	1	8.0326E-06	0.00247612
ILMN_2656854	MYO6	1.149171076	0.0002995	0.01489206	0.0002995	0.01335371	0.0000106	0.00129112	0.000015	0.001927918	1	0.000763113	0.03482416
ILMN_1258652	RBBP2	1.148685264	0.0002995	0.01489206	0.0002995	0.01335371	0.0000026	0.00046493	0.00000949	0.00136995	1	2.24533E-05	0.00440984
ILMN_1245754	CD84	1.148512188	0.0002995	0.01489206	0.0002995	0.01335371	0.0000661	0.0048741	0.00015814	0.009685436	1	0.00042277	0.02466001
ILMN_2780247	LTA	1.147812483	0.00149689	0.03478153	0.00094262	0.02430167	0.0000477	0.00381669	0.000069	0.005349701	1	0.000665544	0.03206944
ILMN_2663930	SLFN1	1.147768768	0.0002995	0.01489206	0.0002995	0.01335371	0.00000138	0.00028053	0.00000835	0.001279253	1	0.000111802	0.01097902
ILMN_3023230	JMJD3	1.147753644	0.0002995	0.01489206	0.0002995	0.01335371	0.00000543	0.00080725	0.0000199	0.002370654	1	0.00011618	0.0112429
ILMN_2764727	ACTN2	1.146764113	0.0002995	0.01489206	0.0002995	0.01335371	1.37E-08	0.00000883	0.00000044	0.000148085	1	2.65234E-05	0.00480383
ILMN_2539295	LOC621968	1.14667536	0.00149689	0.03478153	0.0006399	0.01941092	0.00000448	0.00070872	0.000044	0.003965776	1	0.001797898	0.05487657
ILMN_2448404	SCL0002975.1_346	1.146129707	0.00176049	0.0385938	0.0020184	0.03953445	0.00133016	0.03704155	0.00169107	0.042433629	1	0.002787111	0.07008733
ILMN_1241915	NOTCH1	1.145832115	0.0002995	0.01489206	0.0002995	0.01335371	0.00000308	0.00053349	0.00000333	0.000657593	1	2.24515E-05	0.00440984
ILMN_2605819	EGLN3	1.145595193	0.0006399	0.0211535	0.0006399	0.01941092	0.00000579	0.00084519	0.0000358	0.003445285	1	0.000353739	0.02219068
ILMN_1253699	2900045G02RIK	1.145548347	0.0002995	0.01489206	0.0002995	0.01335371	0.00000247	0.00045603	0.0000131	0.001740513	1	3.12891E-05	0.00543437
ILMN_1244853	LOC100044948	1.14491469	0.0002995	0.01489206	0.0002995	0.01335371	0.00000528	0.0007879	0.000019	0.002312072	1	0.00022037	0.01646479
ILMN_2589871	CD28	1.144678691	0.0006399	0.0211535	0.0002995	0.01335371	0.00000485	0.00074167	0.00000392	0.000746457	1	2.34111E-05	0.00450296
ILMN_2997406	ARL4C	1.144292866	0.00094262	0.02607154	0.0006399	0.01941092	0.0000259	0.00247667	0.0000788	0.005900268	1	0.001686537	0.05325863
ILMN_2860645	GBP6	1.143811908	0.0006399	0.0211535	0.0006399	0.01941092	0.00023405	0.01207808	0.00011452	0.007736431	1	0.000169803	0.01418997
ILMN_1249547	ZFP292	1.143548873	0.0002995	0.01489206	0.0002995	0.01335371	0.0000159	0.00174469	0.0000524	0.004443054	1	0.000163541	0.01374071
ILMN_1236539	PFKL	1.142647393	0.0002995	0.01489206	0.0002995	0.01335371	0.00000177	0.00034525	0.0000425	0.00387062	1	0.000329201	0.02128238
ILMN_2425990	4933421G18RIK	1.142576402	0.0002995	0.01489206	0.0002995	0.01335371	0.0000176	0.00184358	0.0000196	0.002353419	1	5.89742E-06	0.0021116
ILMN_2553041	A130093I21RIK	1.142422921	0.00176049	0.0385938	0.00227139	0.0429166	0.00011916	0.00754608	0.00091734	0.029755562	1	0.000873828	0.03714525
ILMN_1224945	E130113K22RIK	1.141736556	0.0002995	0.01489206	0.0002995	0.01335371	0.00000824	0.0010961	0.0000241	0.002707128	1	1.89821E-05	0.00409055
ILMN_1218525	IL18R1	1.141400055	0.0002995	0.01489206	0.0002995	0.01335371	0.0000071	0.00098878	0.00000253	0.000522839	1	5.52021E-05	0.00760204
ILMN_1243621	A130026C10RIK	1.141355268	0.0002995	0.01489206	0.0002995	0.01335371	0.00014647	0.00871594	0.00067402	0.024761981	1	0.00057968	0.02968357
ILMN_1228608	LOC637353	1.141241268	0.00373333	0.06184411	0.00349473	0.0566205	0.00162544	0.04219715	0.00320971	0.063172249	0	0.005070533	0.09692735
ILMN_1229746	ECM1	1.141034556	0.0002995	0.01489206	0.0002995	0.01335371	0.00000063	0.00015526	0.00000018	0.0000829	1	1.89087E-06	0.00111411
ILMN_2915951	D13ERTD608E	1.140936106	0.0002995	0.01489206	0.0002995	0.01335371	0.0000242	0.0023517	0.0000549	0.004568149	1	5.97852E-05	0.00777325
ILMN_1249864	A630077B13RIK	1.140911297	0.00094262	0.02607154	0.0002995	0.01335371	0.0000339	0.00303141	0.0000306	0.003131644	1	0.000111802	0.01097902
ILMN_2995934	LOC547323	1.140861547	0.0002995	0.01489206	0.0002995	0.01335371	0.00000251	0.00046209	0.00000828	0.001279253	1	3.99889E-05	0.00618393
ILMN_2456391	TCRB-J	1.140797339	0.00176049	0.0385938	0.0002995	0.01335371	0.0000215	0.00216998	0.00010468	0.007215102	1	0.001068077	0.04167292
ILMN_1239469	LEF1	1.140750182	0.0002995	0.01489206	0.0002995	0.01335371	0.00000385	0.00063236	0.0000028	0.000567027	1	9.56597E-06	0.00274856
ILMN_1259463	ANKZF1	1.140723241	0.0002995	0.01489206	0.0002995	0.01335371	1.15E-07	0.0000431	8.51E-07	0.00023576	1	2.27642E-06	0.00127663
ILMN_3142803	CXCL10	1.140155785	0.0032539	0.05678214	0.00301234	0.05155233	0.00516161	0.08343803	0.00230778	0.05128928	0	0.003346676	0.07734743

ILMN_2594768	THA1	1.139893861	0.00149689	0.03478153	0.00094262	0.02430167	0.0000101	0.00124325	0.00018697	0.010823311	1	0.000470028	0.02607676
ILMN_2677207	LOC100047788	1.139882555	0.0056004	0.08017457	0.00490758	0.07073729	0.00128112	0.03625071	0.00280343	0.058355577	0	0.00675613	0.11179438
ILMN_1226048	AI504432	1.13986418	0.0002995	0.01489206	0.0002995	0.01335371	4.96E-07	0.00013044	5.84E-07	0.000181161	1	6.16514E-06	0.0021257
ILMN_1241598	LY116	1.139617809	0.0002995	0.01489206	0.0002995	0.01335371	0.0000304	0.00278339	0.000043	0.003909	1	0.000135352	0.01242731
ILMN_1258272	LOC382646	1.139404236	0.00149689	0.03478153	0.00122569	0.02881591	0.00019446	0.01053711	0.00033198	0.01550964	1	0.001033149	0.04099743
ILMN_1238847	CD3E	1.139135835	0.0006399	0.0211535	0.0002995	0.01335371	0.00000182	0.00035008	0.00000947	0.00136995	1	0.000353739	0.02219068
ILMN_1254218	NISCH	1.138664045	0.0002995	0.01489206	0.0002995	0.01335371	0.0000288	0.00267634	0.00013436	0.00874694	1	7.28705E-05	0.00865281
ILMN_2879858	PRKX	1.138650161	0.0002995	0.01489206	0.0002995	0.01335371	9.55E-12	2.47E-08	4.3E-12	0.00000005	1	1.05033E-08	0.00012222
ILMN_1231490	2410006H16RIK	1.138597457	0.0002995	0.01489206	0.0002995	0.01335371	0.0000613	0.00458827	0.000093	0.006607866	1	9.5799E-05	0.01018072
ILMN_1232707	SAMHD1	1.138552379	0.0002995	0.01489206	0.0002995	0.01335371	0.00000184	0.00035317	2.73E-07	0.000109783	1	8.0326E-06	0.00247612
ILMN_1240592	ALS2CL	1.138470539	0.01404445	0.13554668	0.01142074	0.11750706	0.00241847	0.05412137	0.00804871	0.105414587	0	0.019643191	0.19233384
ILMN_3142602	B3GALT4	1.138320625	0.0002995	0.01489206	0.0002995	0.01335371	1.28E-07	0.0000472	2.85E-07	0.000110081	1	1.72245E-06	0.00108344
ILMN_3031781	ARID5B	1.138169635	0.0006399	0.0211535	0.00094262	0.02430167	0.00017446	0.00971369	0.00037839	0.0167608	1	0.000665544	0.03206944
ILMN_2568028	IL2RG	1.138046812	0.0006399	0.0211535	0.0002995	0.01335371	0.0000163	0.00177372	0.00010898	0.007416137	1	0.000151664	0.01324485
ILMN_1239776	LOC100040243	1.1379032	0.00094262	0.02607154	0.0006399	0.01941092	0.0000766	0.00547181	0.00037845	0.0167608	1	0.000341264	0.02181978
ILMN_1253691	B430201A12RIK	1.137684368	0.0002995	0.01489206	0.0002995	0.01335371	3.76E-07	0.00010665	3.57E-07	0.000132883	1	4.50187E-07	0.00052531
ILMN_1239238	PRKCH	1.137598283	0.0002995	0.01489206	0.0002995	0.01335371	0.00000445	0.00070872	9.27E-07	0.000252346	1	5.30373E-05	0.00748099
ILMN_2663230	SLCO3A1	1.137294887	0.00094262	0.02607154	0.0006399	0.01941092	2.28E-07	0.0000712	0.00000754	0.001205762	1	0.00010758	0.01083883
ILMN_1255869	CATNB	1.137232235	0.0002995	0.01489206	0.0002995	0.01335371	0.0000558	0.0042775	0.0000935	0.006622679	1	0.000135361	0.01242731
ILMN_2847773	OTTMUSG0000000	1.137208625	0.0002995	0.01489206	0.0002995	0.01335371	0.00000407	0.0006631	0.00000411	0.000768531	1	3.39668E-05	0.00570777
ILMN_2945940	RAPGEF4	1.136953118	0.0002995	0.01489206	0.0002995	0.01335371	0.0000964	0.00649408	0.0000445	0.003979315	1	0.000220357	0.01646479
ILMN_2426853	UBD	1.13683555	0.00149689	0.03478153	0.00149689	0.03284241	0.00151895	0.04027676	0.00035471	0.016129651	1	0.001389344	0.04772897
ILMN_2639972	PPP1R3B	1.136776701	0.0002995	0.01489206	0.0002995	0.01335371	0.0000018	0.00034718	0.00000665	0.001105293	1	0.000146035	0.01292295
ILMN_2693461	SSBP2	1.136455877	0.0002995	0.01489206	0.0002995	0.01335371	0.00000811	0.00108443	0.0000104	0.001467743	1	9.95836E-05	0.01046347
ILMN_1258988	IGFBP4	1.136364638	0.00605844	0.08369461	0.00397039	0.06196763	0.00044687	0.01884113	0.00175534	0.043416704	0	0.012677869	0.1539569
ILMN_2509988	LBR	1.136214053	0.0002995	0.01489206	0.0002995	0.01335371	0.00037342	0.01669711	0.00049349	0.020167155	1	0.000317538	0.02078825
ILMN_1230458	IFIT3	1.136194338	0.0020184	0.04200694	0.00149689	0.03284241	0.00399845	0.07166564	0.00197876	0.046801373	0	0.001301631	0.04617913
ILMN_2727235	ANKRD11	1.136184371	0.0020184	0.04200694	0.00122569	0.02881591	0.00057505	0.02210324	0.00110173	0.033170811	1	0.004006777	0.0855913
ILMN_2637714	RASA3	1.135912258	0.0002995	0.01489206	0.0002995	0.01335371	1.38E-07	0.0000492	7.38E-08	0.0000436	1	1.92936E-07	0.00034541
ILMN_2595918	GIMAP7	1.135856716	0.0006399	0.0211535	0.0006399	0.01941092	0.00000021	0.0000667	0.00000695	0.001138958	1	0.000183009	0.01471244
ILMN_1231573	SERPINB1A	1.135730392	0.0002995	0.01489206	0.0002995	0.01335371	9.05E-07	0.00020553	0.00000222	0.000472255	1	3.83949E-05	0.00609954
ILMN_2459155	ZFP238	1.135647435	0.0002995	0.01489206	0.0002995	0.01335371	0.00017162	0.00962449	0.00031671	0.015073371	1	0.000470028	0.02607676
ILMN_1243910	ZFP292	1.13546193	0.0006399	0.0211535	0.0002995	0.01335371	0.00016234	0.00923784	0.00035402	0.016129651	1	0.000712779	0.03334445
ILMN_1222471	GMFG	1.13543581	0.0002995	0.01489206	0.0002995	0.01335371	9.07E-09	0.0000064	9.8E-09	0.0000111	1	5.74828E-07	0.00056929
ILMN_2469190	B230345P09RIK	1.135305336	0.0006399	0.0211535	0.00094262	0.02430167	0.00017922	0.00989578	0.00053924	0.021235038	1	0.000212355	0.01604723
ILMN_2696492	PHF11	1.135183534	0.00094262	0.02607154	0.0006399	0.01941092	0.0000941	0.00638343	0.00015178	0.009420008	1	0.000504223	0.02732257
ILMN_2996904	OBFC2A	1.135148949	0.0002995	0.01489206	0.0002995	0.01335371	0.00000351	0.00059253	0.00000887	0.001330104	1	2.88127E-05	0.00509941
ILMN_1233449	LOC100044430	1.13513543	0.0002995	0.01489206	0.0002995	0.01335371	0.00000334	0.00057008	0.00000669	0.00110836	1	0.000212368	0.01604723
ILMN_1251193	A630084D02RIK	1.134829034	0.0002995	0.01489206	0.0002995	0.01335371	0.00032183	0.01505533	0.0002505	0.012926945	1	0.000379979	0.02324165
ILMN_2758878	TMEM66	1.13478407	0.00276802	0.05133777	0.00176049	0.03635757	0.00043749	0.01861404	0.00091474	0.029733662	0	0.003149577	0.07483876
ILMN_3160137	ALDOC	1.134554634	0.0076447	0.09672601	0.00583002	0.07876136	0.00082471	0.02769675	0.0021101	0.048647455	0	0.012022966	0.14955451
ILMN_1218051	IQGAP2	1.134418217	0.00149689	0.03478153	0.00122569	0.02881591	0.0000255	0.00246014	0.0000551	0.00457056	1	0.000643	0.03157309
ILMN_1230726	5430406J06RIK	1.13436247	0.00122569	0.03054155	0.00094262	0.02430167	0.00022223	0.01167751	0.0008189	0.027904422	1	0.001581552	0.05126497
ILMN_2879614	ZBP1	1.13418419	0.0006399	0.0211535	0.0006399	0.01941092	0.0000132	0.00150968	0.0000283	0.002963331	1	0.000255296	0.01817016
ILMN_2534207	LOC380706	1.133996759	0.0002995	0.01489206	0.0002995	0.01335371	3.59E-08	0.000018	8.2E-09	0.0000103	1	7.68761E-07	0.00070164
ILMN_2659739	IL7R	1.133870404	0.0002995	0.01489206	0.0002995	0.01335371	0.0000625	0.00467003	0.0000102	0.001439966	1	7.88278E-05	0.00901523
ILMN_2958159	ENO1	1.13384821	0.0002995	0.01489206	0.0002995	0.01335371	0.00000265	0.00047116	0.0000399	0.003729707	1	0.000329201	0.02128238

ILMN_1257704	6030458P06RIK	1.133768716	0.0006399	0.0211535	0.0006399	0.01941092	0.0000499	0.00393179	0.00019668	0.011191632	1	0.000197175	0.01547711
ILMN_2477213	LOC100045240	1.133690768	0.0002995	0.01489206	0.0002995	0.01335371	2.65E-07	0.0000787	7.57E-07	0.000219513	1	4.12145E-06	0.00171287
ILMN_2513870	ZAP70	1.133508982	0.0002995	0.01489206	0.0002995	0.01335371	2.43E-07	0.0000731	0.00000252	0.000522839	1	0.000163531	0.01374071
ILMN_1343061	control_ILMN_134	1.133413667	0.05896005	0.29652912	0.05313904	0.27805718	0.0444304	0.27002241	0.05091233	0.282020251	0	0.090139534	0.39515789
ILMN_1258340	TCF12	1.133249325	0.0002995	0.01489206	0.0002995	0.01335371	0.0000229	0.00226216	0.000017	0.002131671	1	2.06483E-05	0.00430994
ILMN_2777019	SPO11	1.133035275	0.0006399	0.0211535	0.0006399	0.01941092	0.00017061	0.00961402	0.000037	0.003539707	1	0.000157497	0.01350097
ILMN_1255907	ARP2	1.132980051	0.0002995	0.01489206	0.0002995	0.01335371	0.0000147	0.00164902	0.0000292	0.003023837	1	4.51564E-05	0.00675851
ILMN_2449620	5830427D02RIK	1.132961187	0.0002995	0.01489206	0.0002995	0.01335371	0.0000477	0.00381669	0.00019019	0.010942585	1	7.57938E-05	0.00879794
ILMN_2477946	SCL0001464.1_61	1.132866527	0.0002995	0.01489206	0.0002995	0.01335371	0.00000865	0.00113789	0.000027	0.002873981	1	0.00040803	0.02413289
ILMN_2627179	ELL3	1.132790682	0.0002995	0.01489206	0.0002995	0.01335371	9.29E-09	0.00000645	1.03E-08	0.0000115	1	1.74307E-07	0.00034541
ILMN_1214318	RASGRP1	1.132335612	0.0006399	0.0211535	0.0002995	0.01335371	0.0000771	0.0054869	0.0000845	0.006173424	1	0.000873828	0.03714525
ILMN_1218206	KLF13	1.132335512	0.0020184	0.04200694	0.00149689	0.03284241	0.00013977	0.00848224	0.00056901	0.022034784	1	0.002540648	0.06640064
ILMN_1233501	C530027B15RIK	1.132246044	0.00122569	0.03054155	0.00122569	0.02881591	0.00014451	0.00864564	0.00060955	0.023104722	1	0.000737547	0.0342621
ILMN_1241522	4921505C17RIK	1.13221457	0.0002995	0.01489206	0.0002995	0.01335371	6.62E-07	0.0001602	0.00000201	0.000441415	1	6.16514E-06	0.0021257
ILMN_1226239	INPP4B	1.132137878	0.00176049	0.0385938	0.00176049	0.03635757	0.00019583	0.01059928	0.00041	0.01769293	1	0.000540669	0.02850419
ILMN_2613422	ITK	1.131935528	0.0006399	0.0211535	0.0006399	0.01941092	0.0000104	0.00127268	0.000056	0.004602895	1	0.000140602	0.01273272
ILMN_2593554	IGTP	1.131930192	0.0002995	0.01489206	0.0002995	0.01335371	0.0000358	0.00314503	0.00000464	0.000834646	1	1.67194E-05	0.0037966
ILMN_1229804	LTA	1.131546852	0.00583002	0.08214635	0.00252097	0.04602629	0.00028612	0.01388718	0.00121075	0.035093672	0	0.008450429	0.12538799
ILMN_2607160	PUM2	1.130377924	0.0006399	0.0211535	0.0002995	0.01335371	0.00000172	0.00033587	0.00000121	0.000298774	1	2.76434E-05	0.00493033
ILMN_3072437	6330500D04RIK	1.130133265	0.00301234	0.05440113	0.00252097	0.04602629	0.00089012	0.02903745	0.0012227	0.035284033	0	0.00210642	0.05997046
ILMN_1251170	AFF4	1.130045502	0.0002995	0.01489206	0.0002995	0.01335371	0.0000524	0.00405887	0.00011408	0.007718214	1	7.0054E-05	0.00846962
ILMN_1246582	LOC436541	1.129946125	0.0006399	0.0211535	0.0006399	0.01941092	0.0000207	0.00211087	0.0000462	0.004074421	1	0.000176289	0.01444673
ILMN_1244891	CST7	1.1298809	0.0002995	0.01489206	0.0002995	0.01335371	0.0000285	0.00265981	0.0000142	0.001859837	1	0.000146035	0.01292295
ILMN_2697693	GRHPR	1.129040446	0.0006399	0.0211535	0.0006399	0.01941092	0.0000147	0.00164902	0.0000385	0.003609572	1	0.000157497	0.01350097
ILMN_1233402	LOC100045981	1.129004666	0.0002995	0.01489206	0.0002995	0.01335371	1.69E-07	0.0000566	0.00000129	0.000312387	1	7.03988E-06	0.00230764
ILMN_1258864	BC106179	1.128947865	0.0002995	0.01489206	0.0006399	0.01941092	0.00043723	0.01861404	0.00059166	0.022629221	1	0.000317538	0.02078825
ILMN_1234796	HSD17B12	1.128868369	0.0002995	0.01489206	0.0002995	0.01335371	0.0000811	0.00570333	0.00021329	0.011819303	1	0.000197175	0.01547711
ILMN_1236595	SLA2	1.128559293	0.00176049	0.0385938	0.00122569	0.02881591	0.0000231	0.00227606	0.00024722	0.012817366	1	0.001344859	0.0469611
ILMN_1241952	6230415M23RIK	1.12852499	0.0002995	0.01489206	0.0006399	0.01941092	0.00028485	0.01386905	0.00098023	0.030953762	1	0.00148248	0.04961268
ILMN_2657980	FAAH	1.128386309	0.0002995	0.01489206	0.0002995	0.01335371	0.0000342	0.00304391	0.00014089	0.009031912	1	0.00040803	0.02413289
ILMN_2745614	FAM134B	1.127986989	0.0002995	0.01489206	0.0002995	0.01335371	0.0000227	0.00225688	0.000034	0.003321814	1	0.000264806	0.01861919
ILMN_1240415	LOC234987	1.127947991	0.0002995	0.01489206	0.0002995	0.01335371	0.0000121	0.00143247	0.0000715	0.005501275	1	0.000163531	0.01374071
ILMN_2552490	6720463L11RIK	1.127757726	0.0006399	0.0211535	0.0002995	0.01335371	0.0000289	0.00267683	0.00012185	0.008102409	1	0.000317538	0.02078825
ILMN_2729447	9030612M13RIK	1.12772184	0.0002995	0.01489206	0.0002995	0.01335371	0.00000038	0.0001073	0.00000154	0.000360893	1	1.24004E-05	0.00322459
ILMN_1233293	GBP1	1.127491461	0.0002995	0.01489206	0.0002995	0.01335371	0.00077034	0.02679885	0.0000253	0.002787107	1	3.39668E-05	0.00570777
ILMN_1236105	FYB	1.127293421	0.00176049	0.0385938	0.0020184	0.03953445	0.00046297	0.01920664	0.00246862	0.053569604	0	0.003663228	0.08166297
ILMN_3009860	SELL	1.126985915	0.0006399	0.0211535	0.0002995	0.01335371	0.00000258	0.00046493	0.0000101	0.001437553	1	6.47271E-05	0.00803428
ILMN_1217929	LOC667005	1.126757091	0.00094262	0.02607154	0.00094262	0.02430167	0.00030191	0.01442973	0.00061251	0.023197995	1	0.000763113	0.03482416
ILMN_1219896	LOC623121	1.126643386	0.0002995	0.01489206	0.0006399	0.01941092	0.00017252	0.00966351	0.00036014	0.0162751	1	0.000169803	0.01418997
ILMN_2808485	GBP10	1.126535797	0.00094262	0.02607154	0.00094262	0.02430167	0.00089514	0.02913696	0.00032196	0.015214362	1	0.000903743	0.03800048
ILMN_2628271	LOC100045967	1.126530154	0.00122569	0.03054155	0.0006399	0.01941092	0.00000934	0.00118696	0.00014347	0.009094873	1	0.001741399	0.05411008
ILMN_2959272	RNU6	1.126488141	0.0002995	0.01489206	0.0002995	0.01335371	0.0001271	0.00781497	0.0000785	0.005894011	1	5.52021E-05	0.00760204
ILMN_1240857	COX7A1	1.126488113	0.0002995	0.01489206	0.0002995	0.01335371	0.00000712	0.00098878	0.0000106	0.001479487	1	1.08955E-05	0.00300091
ILMN_1248837	TBXA2R	1.126308353	0.0006399	0.0211535	0.0006399	0.01941092	0.0000496	0.00391795	0.0000556	0.004598957	1	0.00010758	0.01083883
ILMN_1213986	LOC380617	1.126269609	0.0002995	0.01489206	0.0002995	0.01335371	0.0000257	0.00247459	0.0000184	0.002261567	1	2.24533E-05	0.00440984
ILMN_2565089	A830083H19RIK	1.126188031	0.0002995	0.01489206	0.0002995	0.01335371	0.0000412	0.00347143	0.000057	0.00465062	1	3.99889E-05	0.00618393
ILMN_2756628	CMC1	1.125722229	0.0002995	0.01489206	0.0002995	0.01335371	1.76E-09	0.00000151	6.75E-09	0.00000872	1	3.51784E-07	0.00045485

ILMN_2689307	SPNB2	1.125305551	0.0002995	0.01489206	0.0002995	0.01335371	0.0000723	0.00525285	0.00023598	0.01249632	1	0.000284828	0.01943975
ILMN_2551741	0610010I05RIK	1.124918642	0.0006399	0.0211535	0.0006399	0.01941092	0.00046313	0.01920664	0.00104266	0.032055996	1	0.000540698	0.02850419
ILMN_1343062	control_ILMN_134	1.124836817	0.06518171	0.31189827	0.05958295	0.29527363	0.05222749	0.29304733	0.05948765	0.305188121	0	0.168994973	0.52187414
ILMN_2749364	LOC382646	1.124580104	0.00276802	0.05133777	0.00176049	0.03635757	0.0000498	0.00393109	0.00024533	0.01278781	0	0.002963349	0.07240684
ILMN_2784272	IFNGR2	1.124504822	0.0020184	0.04200694	0.00176049	0.03635757	0.0008594	0.02845121	0.0016295	0.041583456	1	0.000903743	0.03800048
ILMN_1225348	FAM102A	1.12448091	0.0002995	0.01489206	0.0002995	0.01335371	0.00000714	0.00098905	0.0000248	0.002755904	1	0.000189968	0.01508948
ILMN_2630739	PHF20L1	1.124360297	0.00094262	0.02607154	0.00149689	0.03284241	0.00051915	0.02079588	0.00041925	0.017887063	1	0.000393771	0.02371136
ILMN_2418366	6720427H10RIK	1.124259069	0.0002995	0.01489206	0.0002995	0.01335371	0.00014538	0.00867674	0.00026831	0.013575239	1	0.000540727	0.02850419
ILMN_2846731	1110059E24RIK	1.124049613	0.0002995	0.01489206	0.0002995	0.01335371	2.88E-08	0.0000149	1.45E-07	0.0000709	1	2.15328E-05	0.0043202
ILMN_2594855	PDPK1	1.124023837	0.0002995	0.01489206	0.0002995	0.01335371	0.0000466	0.00377453	0.0000558	0.004598957	1	0.000189956	0.01508948
ILMN_1246543	SIAT7C	1.124022495	0.0002995	0.01489206	0.0002995	0.01335371	0.00032001	0.01501554	0.00045251	0.018972559	1	0.000737547	0.0342621
ILMN_2614884	PJA1	1.123647984	0.0002995	0.01489206	0.0002995	0.01335371	0.00000151	0.00030356	0.00000406	0.000761994	1	1.74444E-05	0.00390377
ILMN_1250418	NPC1	1.123625032	0.0002995	0.01489206	0.0002995	0.01335371	1.39E-07	0.0000492	2.76E-07	0.000109783	1	2.27642E-06	0.00127663
ILMN_2706514	LOC100046608	1.123601186	0.00094262	0.02607154	0.0006399	0.01941092	0.00010046	0.00665173	0.00032888	0.015447583	1	0.001581552	0.05126497
ILMN_1241924	ARL6IP5	1.123582409	0.0002995	0.01489206	0.0002995	0.01335371	0.0000299	0.00274992	0.00010627	0.007284834	1	0.00027463	0.01910904
ILMN_2750265	ELMO1	1.123418741	0.00122569	0.03054155	0.00122569	0.02881591	0.0004071	0.01774258	0.00092146	0.02980611	1	0.001915982	0.05666025
ILMN_2712895	4631423B10RIK	1.123402203	0.0002995	0.01489206	0.0002995	0.01335371	0.0000422	0.0035217	0.00010479	0.007215102	1	0.000176289	0.01444673
ILMN_2719139	AB124611	1.122548641	0.00122569	0.03054155	0.0006399	0.01941092	0.00023483	0.0121047	0.00029401	0.014330244	1	0.001581552	0.05126497
ILMN_2692986	2810410P22RIK	1.122423336	0.00149689	0.03478153	0.00122569	0.02881591	0.00015964	0.00916202	0.00016472	0.009931795	1	0.0007895	0.03543767
ILMN_1228333	PRF1	1.122189532	0.00276802	0.05133777	0.00122569	0.02881591	0.0001055	0.00691623	0.00012319	0.008156571	0	0.002173782	0.0607706
ILMN_2940446	DGKA	1.122160698	0.00176049	0.0385938	0.00149689	0.03284241	0.0000799	0.00565291	0.00044116	0.018633965	1	0.003449313	0.07881943
ILMN_3034381	NUP88	1.121988063	0.00094262	0.02607154	0.00094262	0.02430167	0.00011496	0.00735062	0.00016939	0.010108673	1	0.000246108	0.01770572
ILMN_2668387	CGGBP1	1.121946931	0.0002995	0.01489206	0.0002995	0.01335371	0.00000034	0.0000984	1.68E-07	0.000078	1	3.59866E-06	0.00158025
ILMN_2592953	SCG5	1.121946089	0.0002995	0.01489206	0.0002995	0.01335371	0.000026	0.00247667	0.0000347	0.003370075	1	0.000228655	0.01684049
ILMN_1228867	A130082M07RIK	1.121929865	0.00094262	0.02607154	0.0002995	0.01335371	0.00000462	0.00072482	0.0000117	0.001595024	1	0.00042277	0.02466001
ILMN_2785454	HIST2H2AB	1.121848738	0.00898742	0.10547593	0.00965407	0.10652405	0.00889504	0.11365284	0.01039259	0.121665992	0	0.049191671	0.30108149
ILMN_2773900	GLIPR2	1.1217158	0.0006399	0.0211535	0.0006399	0.01941092	6.02E-07	0.00014992	0.00000244	0.000512485	1	3.83949E-05	0.00609954
ILMN_2647102	ACTL6A	1.121390591	0.0002995	0.01489206	0.0002995	0.01335371	0.00000884	0.00115212	0.0000424	0.00387062	1	7.57938E-05	0.00879794
ILMN_1256574	NCOA2	1.121377157	0.00094262	0.02607154	0.00094262	0.02430167	0.0000493	0.00391165	0.00022291	0.012129499	1	0.00040803	0.02413289
ILMN_1243902	A530024C08RIK	1.12112103	0.0020184	0.04200694	0.00176049	0.03635757	0.00045505	0.01903079	0.00088129	0.029196677	1	0.00305523	0.07341857
ILMN_1343048	control_ILMN_134	1.120964441	0.0006399	0.0211535	0.0006399	0.01941092	0.00023856	0.01218903	0.00027171	0.013620278	1	0.000934606	0.03863507
ILMN_2878979	TNFAIP8L2	1.120676477	0.0002995	0.01489206	0.0002995	0.01335371	4.64E-07	0.00012621	0.00000373	0.000722783	1	1.74444E-05	0.00390377
ILMN_2887619	RPS25	1.120128473	0.03241096	0.21464233	0.03788279	0.2312766	0.02525122	0.20197503	0.03226412	0.224678675	0	0.039320852	0.27099019
ILMN_2678724	DUSP10	1.119986223	0.0006399	0.0211535	0.0002995	0.01335371	0.00021616	0.0114725	0.00028764	0.014123395	1	0.000379979	0.02324165
ILMN_1244135	ARPC5	1.119864481	0.00301234	0.05440113	0.00373333	0.05925673	0.00703752	0.09959734	0.00558971	0.086699245	0	0.00450999	0.09155774
ILMN_2651297	4632428N05RIK	1.119607561	0.0002995	0.01489206	0.0002995	0.01335371	0.00000985	0.00121884	0.00000212	0.00045645	1	1.35117E-05	0.00345566
ILMN_2822842	1600014C10RIK	1.119392625	0.0002995	0.01489206	0.0002995	0.01335371	0.0000173	0.00183184	0.00000567	0.00097714	1	1.97985E-05	0.00420804
ILMN_2665545	RIN3	1.119281709	0.0002995	0.01489206	0.0002995	0.01335371	0.0000502	0.0039435	0.0000406	0.003782136	1	0.000246108	0.01770572
ILMN_2703321	ANKZF1	1.119253	0.0002995	0.01489206	0.0002995	0.01335371	0.0000123	0.0014435	0.0000441	0.003965776	1	0.000146035	0.01292295
ILMN_1259917	D330001F19RIK	1.119179745	0.0002995	0.01489206	0.0002995	0.01335371	0.0002103	0.01126316	0.00034508	0.015942739	1	0.000353739	0.02219068
ILMN_1237871	AMPD1	1.119072973	0.0002995	0.01489206	0.0002995	0.01335371	0.000036	0.00314503	0.0000107	0.001483462	1	4.70154E-05	0.00688184
ILMN_1256950	NEURL2	1.11903277	0.0006399	0.0211535	0.0006399	0.01941092	0.0000169	0.00180017	0.0000192	0.002327044	1	3.83949E-05	0.00609954
ILMN_1228020	1500010G04RIK	1.118985348	0.00122569	0.03054155	0.00094262	0.02430167	0.0000866	0.00599563	0.00023442	0.012474872	1	0.000934606	0.03863507
ILMN_1227573	IRF7	1.118870281	0.00397039	0.064249	0.00397039	0.06196763	0.0023181	0.05257933	0.00445393	0.076746435	0	0.002387591	0.06387081
ILMN_2726315	SDF4	1.118652369	0.00149689	0.03478153	0.0006399	0.01941092	0.00000926	0.00118448	0.0000286	0.002983758	1	0.000621233	0.03109305
ILMN_1227907	GMFG	1.11859249	0.0002995	0.01489206	0.0002995	0.01335371	1.41E-08	0.00000898	1.13E-07	0.0000599	1	7.03866E-06	0.00230764
ILMN_2881296	TMEM66	1.118516263	0.0002995	0.01489206	0.0002995	0.01335371	0.00000179	0.00034718	0.00000451	0.000814057	1	1.29447E-05	0.00332893

ILMN_3043245	JMJD1A	1.118512017	0.0002995	0.01489206	0.0002995	0.01335371	2.31E-07	0.0000712	5.23E-07	0.000168884	1	3.93982E-06	0.00166715
ILMN_2580159	C230070D10RIK	1.118494179	0.00094262	0.02607154	0.00094262	0.02430167	0.00055671	0.02167037	0.00125356	0.035750241	1	0.000712779	0.03334445
ILMN_1252472	ITK	1.118457931	0.00227139	0.04545806	0.00276802	0.04845153	0.0005963	0.02265805	0.00234006	0.051632853	0	0.001856078	0.05577459
ILMN_2828916	FRMD6	1.11830741	0.0006399	0.0211535	0.0006399	0.01941092	0.00017343	0.00968113	0.0000582	0.004700168	1	0.000182997	0.01471244
ILMN_1257771	LOC638301	1.118249781	0.00149689	0.03478153	0.00094262	0.02430167	0.0000793	0.00561815	0.0000839	0.006145701	1	0.001218998	0.0445025
ILMN_3002095	IL27RA	1.118221343	0.0006399	0.0211535	0.0006399	0.01941092	0.0000149	0.00166378	0.0000489	0.004233399	1	0.000621233	0.03109305
ILMN_2658961	DGKA	1.118166028	0.00176049	0.0385938	0.00176049	0.03635757	0.00026591	0.01325214	0.00064942	0.024048059	1	0.002314175	0.06295874
ILMN_2038771	control_ILMN_203	1.118161322	0.06020572	0.30013907	0.05480359	0.28252036	0.05700779	0.30549638	0.05139364	0.283318913	0	0.154914896	0.50337338
ILMN_2981801	HIST1H2AG	1.118065046	0.00094262	0.02607154	0.0006399	0.01941092	0.00037162	0.01664832	0.00020154	0.011374568	1	0.000504223	0.02732257
ILMN_1249710	E030038D23RIK	1.117909411	0.0002995	0.01489206	0.0002995	0.01335371	0.0000376	0.00323771	0.00015401	0.009469751	1	0.000306263	0.02048222
ILMN_2943057	ARL5C	1.117880079	0.00176049	0.0385938	0.00094262	0.02430167	0.00042833	0.01837561	0.00044307	0.018680938	1	0.000763113	0.03482416
ILMN_1235856	8030474H12RIK	1.117810336	0.0002995	0.01489206	0.0002995	0.01335371	0.00024238	0.01232448	0.00022154	0.012090825	1	0.000103509	0.01061242
ILMN_1247942	MGEA5	1.117806646	0.0006399	0.0211535	0.0006399	0.01941092	0.00030694	0.0145343	0.00051962	0.020743454	1	0.00042277	0.02466001
ILMN_1258509	SIT1	1.117432738	0.0006399	0.0211535	0.0002995	0.01335371	0.00015174	0.00888405	0.00010235	0.007068104	1	0.000237231	0.01736224
ILMN_2544056	HBB-B1	1.117213432	0.03914176	0.23704991	0.03599148	0.22485976	0.02097723	0.18409981	0.02922158	0.212190751	0	0.025142431	0.2182235
ILMN_2729953	PPM1B	1.117036433	0.00537037	0.07818332	0.00537037	0.07497442	0.00364121	0.06763268	0.00503541	0.081966426	0	0.008450429	0.12538799
ILMN_1219602	LOC100048770	1.116440805	0.00397039	0.064249	0.00373333	0.05925673	0.00631793	0.09355312	0.00215116	0.049131535	0	0.004251793	0.08882774
ILMN_2681670	VPS37B	1.116406759	0.0002995	0.01489206	0.0002995	0.01335371	0.00000824	0.0010961	0.0000174	0.002162819	1	6.22097E-05	0.00789013
ILMN_1234955	6430573H23RIK	1.116406299	0.00176049	0.0385938	0.0020184	0.03953445	0.00074236	0.02603981	0.00161499	0.04134913	1	0.002387591	0.06387081
ILMN_2582659	E030040J04RIK	1.116391042	0.0002995	0.01489206	0.0002995	0.01335371	0.0000266	0.00251609	0.000057	0.00465062	1	0.00010758	0.01083883
ILMN_1252514	C920016N10RIK	1.116354745	0.00176049	0.0385938	0.00122569	0.02881591	0.00015113	0.00885986	0.00043359	0.018347587	1	0.0007895	0.03543767
ILMN_2617433	ACTB	1.11629809	0.00397039	0.064249	0.0032539	0.05432415	0.00287066	0.05995273	0.00272663	0.057221177	0	0.00553098	0.10148188
ILMN_2738972	CNOT4	1.116182237	0.0002995	0.01489206	0.0002995	0.01335371	0.0000107	0.00130299	0.00000896	0.00133296	1	2.65234E-05	0.00480383
ILMN_2553280	4732470M22RIK	1.1161327	0.0002995	0.01489206	0.0002995	0.01335371	0.00000649	0.00093461	0.0000318	0.003192608	1	0.000111802	0.01097902
ILMN_1238725	C130086J11RIK	1.116108151	0.01382667	0.13456133	0.01513108	0.13869555	0.01286055	0.14095122	0.01459273	0.14770671	0	0.023367993	0.21022612
ILMN_2998813	SEMA4F	1.115968974	0.0002995	0.01489206	0.0002995	0.01335371	0.0000207	0.00211087	0.0000384	0.003609572	1	8.86334E-05	0.00982291
ILMN_1236445	9130227N12RIK	1.115922245	0.00252097	0.04839275	0.00176049	0.03635757	0.00096123	0.03064541	0.0019356	0.046142977	1	0.00305523	0.07341857
ILMN_1220893	ZFP281	1.115869505	0.0002995	0.01489206	0.0002995	0.01335371	0.00000124	0.00026043	8.12E-07	0.000227616	1	5.3945E-06	0.00202516
ILMN_2417398	IGHV10S1_AF0644	1.115826459	0.00490758	0.07399298	0.0056004	0.0767776	0.00919199	0.1159197	0.0048635	0.080501378	0	0.005531174	0.10148188
ILMN_1238893	LIME1	1.115781178	0.00176049	0.0385938	0.0006399	0.01941092	0.00012493	0.00775324	0.00014361	0.009094873	1	0.001141234	0.04287409
ILMN_2706550	SUSD3	1.115744092	0.00122569	0.03054155	0.00094262	0.02430167	0.00014378	0.00861922	0.00016702	0.010005399	1	0.000816732	0.0360345
ILMN_1242235	TOP2A	1.115488708	0.0006399	0.0211535	0.0002995	0.01335371	9.23E-07	0.00020859	0.00000447	0.00081037	1	7.28705E-05	0.00865281
ILMN_2638923	RN18S	1.115471516	0.00301234	0.05440113	0.00583002	0.07876136	0.00712305	0.10016817	0.00794885	0.10463667	0	0.002620495	0.06768933
ILMN_1232894	ZNRF1	1.115445926	0.0002995	0.01489206	0.0002995	0.01335371	0.0000217	0.00217431	0.0000588	0.004724126	1	0.00010758	0.01083883
ILMN_1218799	EMB	1.115430499	0.0002995	0.01489206	0.0002995	0.01335371	0.00000545	0.00080859	0.00000586	0.00100296	1	1.04339E-05	0.00292569
ILMN_1257209	WIPF1	1.115376002	0.0002995	0.01489206	0.0002995	0.01335371	0.0000145	0.00163779	0.000022	0.002530716	1	9.57926E-05	0.01018072
ILMN_2711705	DUSP11	1.115060696	0.0002995	0.01489206	0.0002995	0.01335371	1.99E-07	0.0000652	0.0000011	0.000288061	1	3.99889E-05	0.00618393
ILMN_1236202	C430015M08RIK	1.114991211	0.0006399	0.0211535	0.00094262	0.02430167	0.00030256	0.01442973	0.00099864	0.031261571	1	0.002041151	0.05875662
ILMN_1233474	IL2RA	1.114952254	0.00809366	0.10014632	0.00537037	0.07497442	0.00167948	0.04316669	0.00320035	0.063041403	0	0.005220076	0.09861156
ILMN_2762863	AI606181	1.114892504	0.0006399	0.0211535	0.0002995	0.01335371	0.00019259	0.01044808	0.00019794	0.011235697	1	0.0007895	0.03543767
ILMN_2644350	THY1	1.114766581	0.00094262	0.02607154	0.0006399	0.01941092	0.0000457	0.00372533	0.00012026	0.008031164	1	0.002463032	0.06525142
ILMN_1255860	KLRD1	1.114664485	0.0002995	0.01489206	0.0002995	0.01335371	0.00017959	0.00990444	0.0000691	0.005350074	1	0.000183009	0.01471244
ILMN_2636403	AXUD1	1.11465607	0.0002995	0.01489206	0.0002995	0.01335371	9.85E-07	0.00021734	6.14E-07	0.00018775	1	1.08955E-05	0.00300091
ILMN_2918002	GBP3	1.114435116	0.00094262	0.02607154	0.0002995	0.01335371	0.00057359	0.02206532	0.00015319	0.009469751	1	0.0007895	0.03543767
ILMN_2649068	IRF1	1.114384547	0.00719408	0.09294718	0.00719408	0.09003289	0.00662885	0.09604617	0.00588889	0.088967898	0	0.006383386	0.10923805
ILMN_1215939	TRBV13-1_M1561	1.114252325	0.0006399	0.0211535	0.0006399	0.01941092	0.0000276	0.00258118	0.000058	0.004693744	1	0.000111795	0.01097902
ILMN_2520264	2010016I18RIK	1.114246403	0.00122569	0.03054155	0.00149689	0.03284241	0.00065214	0.02390174	0.00109041	0.033000801	1	0.001389407	0.04772897

ILMN_1220889	NBR1	1.114192214	0.0002995	0.01489206	0.0002995	0.01335371	0.00041846	0.01811912	0.0000489	0.004233399	1	0.000103509	0.01061242
ILMN_2706803	CRLF3	1.114104774	0.0002995	0.01489206	0.0002995	0.01335371	0.00012104	0.00760514	0.0000382	0.003601497	1	0.000212368	0.01604723
ILMN_2751603	PHXR4	1.11385586	0.00876432	0.1043511	0.01317262	0.12756294	0.00581702	0.08937751	0.01967293	0.172805787	0	0.017311316	0.18018556
ILMN_1240030	NFATC3	1.113638258	0.0002995	0.01489206	0.0002995	0.01335371	0.0000187	0.00193661	0.000099	0.006922165	1	0.000204639	0.01592867
ILMN_1242390	ACTN4	1.113610426	0.0067415	0.08943186	0.00537037	0.07497442	0.00225911	0.05195492	0.00310551	0.061933186	0	0.002963349	0.07240684
ILMN_2510694	NME7	1.113521644	0.0020184	0.04200694	0.00176049	0.03635757	0.00018011	0.0099096	0.0002504	0.012926945	1	0.002540648	0.06640064
ILMN_1258466	LOC380623	1.113479163	0.00149689	0.03478153	0.00122569	0.02881591	0.0000863	0.00599563	0.00049148	0.020138305	1	0.001104095	0.04229821
ILMN_1252089	NFATC3	1.113257321	0.00094262	0.02607154	0.0006399	0.01941092	0.00044981	0.01893053	0.00134792	0.037368442	1	0.001344859	0.0469611
ILMN_2522571	SETD7	1.113080478	0.0002995	0.01489206	0.0002995	0.01335371	0.0001715	0.00962449	0.0000765	0.005770769	1	1.81978E-05	0.00399552
ILMN_2593002	ST6GAL2	1.113003988	0.0002995	0.01489206	0.0002995	0.01335371	0.0000472	0.00380085	0.00000968	0.001390556	1	4.89467E-05	0.00705363
ILMN_1248379	EG434077	1.112625375	0.0002995	0.01489206	0.0002995	0.01335371	0.0000115	0.00138752	0.000012	0.001629081	1	1.53585E-05	0.00359242
ILMN_1223119	BCL11B	1.112508226	0.0020184	0.04200694	0.00122569	0.02881591	0.0000582	0.00441806	0.00012873	0.008463041	1	0.000688785	0.03268184
ILMN_3059798	FOXK1	1.112313504	0.00122569	0.03054155	0.00094262	0.02430167	0.00017816	0.00984919	0.00028068	0.013898949	1	0.000688785	0.03268184
ILMN_2534794	LOC236170	1.112310228	0.0051392	0.07619761	0.00420612	0.06441203	0.00030301	0.01443599	0.00092888	0.029963118	0	0.002620495	0.06768933
ILMN_2618549	RAB7	1.112121637	0.0006399	0.0211535	0.00122569	0.02881591	0.00187936	0.0464569	0.00194545	0.046343295	1	0.001915982	0.05666025
ILMN_2468405	5630401D06RIK	1.111986642	0.0002995	0.01489206	0.0002995	0.01335371	2.09E-07	0.0000667	0.00000224	0.00047443	1	9.99008E-06	0.00281847
ILMN_1258587	LOC100044376	1.111863958	0.0002995	0.01489206	0.0002995	0.01335371	0.00000504	0.00076175	0.00000641	0.001075031	1	2.76413E-05	0.00493033
ILMN_1218732	2810426P10RIK	1.11161873	0.0002995	0.01489206	0.0002995	0.01335371	0.0000688	0.00501883	0.00013675	0.008839595	1	0.000183009	0.01471244
ILMN_1237980	0610010D24RIK	1.111616983	0.0006399	0.0211535	0.0002995	0.01335371	0.00014715	0.00873651	0.00031915	0.015112162	1	0.000486846	0.02669165
ILMN_1214874	LOC386068	1.111606821	0.00094262	0.02607154	0.0002995	0.01335371	0.0000748	0.0053805	0.0001023	0.007068104	1	0.000844832	0.03651291
ILMN_1220418	HCST	1.111606518	0.0002995	0.01489206	0.0002995	0.01335371	0.0001505	0.00885642	0.0000483	0.004205779	1	5.74463E-05	0.00761864
ILMN_2550291	2310032M22RIK	1.111606315	0.0006399	0.0211535	0.0006399	0.01941092	0.00010944	0.00711397	0.00012106	0.008061295	1	0.000135361	0.01242731
ILMN_1234202	PHIP	1.111345184	0.0002995	0.01489206	0.00094262	0.02430167	0.00090293	0.02928231	0.00134681	0.037363102	1	0.000486846	0.02669165
ILMN_2426949	TNFRSF14	1.111293325	0.0006399	0.0211535	0.0006399	0.01941092	0.0000768	0.00547429	0.00020508	0.011473406	1	0.000453754	0.02560106
ILMN_2497395	9130004J05RIK	1.111130133	0.00122569	0.03054155	0.00122569	0.02881591	0.00027804	0.01366608	0.00076296	0.026721993	1	0.002106509	0.05997046
ILMN_2715730	SPN	1.111033738	0.0002995	0.01489206	0.0006399	0.01941092	0.0000115	0.00138491	0.0000749	0.005687727	1	0.000284828	0.01943975
ILMN_1217606	1500005K14RIK	1.110936144	0.00122569	0.03054155	0.00149689	0.03284241	0.00036072	0.01628339	0.00024226	0.012705581	1	0.000737547	0.0342621
ILMN_1216313	STIM1	1.110931979	0.00122569	0.03054155	0.00227139	0.0429166	0.00138944	0.03799885	0.00340804	0.065686921	0	0.004644684	0.0931111
ILMN_1252761	DRG1	1.110887212	0.00122569	0.03054155	0.0006399	0.01941092	0.00096761	0.03080362	0.00048307	0.019916078	1	0.000486846	0.02669165
ILMN_2710312	LOC100046650	1.110811588	0.0002995	0.01489206	0.0002995	0.01335371	0.00000957	0.00121086	0.0000519	0.004442214	1	0.000470003	0.02607676
ILMN_1232668	MAD	1.110784132	0.0002995	0.01489206	0.0002995	0.01335371	0.00026552	0.01324676	0.00020949	0.011649906	1	0.000212368	0.01604723
ILMN_2593774	1190002H23RIK	1.110704	0.0002995	0.01489206	0.0002995	0.01335371	0.00000489	0.00074347	0.00000986	0.001403781	1	6.47271E-05	0.00803428
ILMN_2559724	A130014O09RIK	1.110598097	0.01142074	0.12058349	0.00876432	0.10074305	0.00510266	0.08281496	0.00678734	0.095622483	0	0.005692914	0.10310819
ILMN_3002505	ABHD8	1.110530454	0.00094262	0.02607154	0.00094262	0.02430167	0.0000941	0.00638343	0.00019979	0.011313575	1	0.000540727	0.02850419
ILMN_2441724	9430014F16RIK	1.110454831	0.0006399	0.0211535	0.0006399	0.01941092	0.00023109	0.01201016	0.00020319	0.011438788	1	0.000665544	0.03206944
ILMN_1229005	TRAT1	1.110421282	0.0006399	0.0211535	0.0006399	0.01941092	0.00027271	0.01347531	0.00019498	0.011135911	1	0.001104043	0.04229821
ILMN_1229518	B230340J04RIK	1.11037499	0.0002995	0.01489206	0.0002995	0.01335371	0.00000774	0.0010503	0.00000785	0.001234703	1	9.56597E-06	0.00274856
ILMN_2576568	D130062J21RIK	1.110225832	0.00176049	0.0385938	0.00276802	0.04845153	0.0029345	0.06072226	0.00575947	0.08793067	0	0.004510321	0.09155774
ILMN_2491182	A130010C12RIK	1.110126472	0.01426212	0.13687557	0.0179397	0.15296839	0.0043924	0.07547173	0.01868086	0.168124091	0	0.037563093	0.2654797
ILMN_2484278	9930031P18RIK	1.110094091	0.00252097	0.04839275	0.00301234	0.05155233	0.00533746	0.08531507	0.00968357	0.116862873	0	0.012022966	0.14955451
ILMN_2827780	D14ERTD668E	1.11008286	0.0006399	0.0211535	0.0002995	0.01335371	0.0000427	0.00354604	0.0000575	0.004674319	1	0.000642967	0.03157309
ILMN_3112873	TXNIP	1.110031984	0.00094262	0.02607154	0.0006399	0.01941092	0.0001431	0.00861123	0.0002438	0.012729351	1	0.001141234	0.04287409
ILMN_3117602	CD6	1.109929013	0.0002995	0.01489206	0.0002995	0.01335371	0.00000663	0.00094987	0.0000261	0.002837023	1	0.000197163	0.01547711
ILMN_1233424	LBCL1	1.109898196	0.0002995	0.01489206	0.0002995	0.01335371	0.0000427	0.00354604	0.0000532	0.004485638	1	0.000103509	0.01061242
ILMN_2681601	SLC44A2	1.109888463	0.010097	0.11285122	0.00854165	0.09937884	0.00254344	0.05584417	0.0068766	0.096328868	0	0.009432203	0.13248473
ILMN_2762956	SPCS2	1.109838126	0.0002995	0.01489206	0.0002995	0.01335371	0.0000411	0.00346811	0.00013104	0.00859081	1	0.000189968	0.01508948
ILMN_2632230	D2ERTD391E	1.109720922	0.0002995	0.01489206	0.0002995	0.01335371	0.00000699	0.00098038	0.0000266	0.002856495	1	0.000317538	0.02078825

ILMN_3052501	CD27	1.109550882	0.00094262	0.02607154	0.0006399	0.01941092	0.0000571	0.00436027	0.00011777	0.007898943	1	0.000966442	0.03935694
ILMN_2615096	DPP4	1.109531905	0.0002995	0.01489206	0.0002995	0.01335371	4.24E-07	0.00011758	2.57E-07	0.000106375	1	2.49646E-06	0.00133566
ILMN_2629112	ASAH3L	1.109478785	0.0002995	0.01489206	0.0002995	0.01335371	0.0000279	0.00260327	0.0000227	0.002596277	1	3.53859E-05	0.0058616
ILMN_1254916	LOC386508	1.109314765	0.00094262	0.02607154	0.0006399	0.01941092	0.0000268	0.00252935	0.00029189	0.014258943	1	0.002106509	0.05997046
ILMN_2686115	RAPGEF6	1.109219239	0.00605844	0.08369461	0.00444101	0.06659434	0.00124244	0.03553479	0.00286075	0.059099453	0	0.008219665	0.12365894
ILMN_3153010	SLITRK5	1.109095163	0.0002995	0.01489206	0.0002995	0.01335371	0.00015814	0.00910989	0.0000467	0.004101953	1	5.97852E-05	0.00777325
ILMN_2571616	C430002D13RIK	1.109088506	0.00122569	0.03054155	0.0020184	0.03953445	0.00120471	0.03493809	0.00223335	0.05034168	0	0.001797898	0.05487657
ILMN_1231785	HDAC2	1.10904434	0.0006399	0.0211535	0.0002995	0.01335371	0.00011044	0.00713983	0.00026456	0.013458572	1	0.000237231	0.01736224
ILMN_1221831	TCFAP2E	1.10874714	0.00176049	0.0385938	0.00176049	0.03635757	0.0006064	0.02285402	0.00061856	0.023351316	1	0.001344859	0.0469611
ILMN_2646456	RNPC2	1.108556752	0.00397039	0.064249	0.00349473	0.0566205	0.00206214	0.04929958	0.00297458	0.060346491	0	0.003346676	0.07734743
ILMN_2504686	MT-ATP6	1.108358727	0.00876432	0.1043511	0.00898742	0.10212898	0.006843	0.09776578	0.01129715	0.127943658	0	0.013719454	0.16025079
ILMN_2712867	TIMP2	1.108193843	0.0002995	0.01489206	0.0002995	0.01335371	0.0000462	0.00374496	0.0000657	0.005137493	1	5.74504E-05	0.00761864
ILMN_1234006	LOC277136	1.10816163	0.00373333	0.06184411	0.0020184	0.03953445	0.0000764	0.00546326	0.00034246	0.015876812	0	0.001104095	0.04229821
ILMN_2965669	XLR4A	1.108141291	0.0002995	0.01489206	0.0002995	0.01335371	0.00000486	0.00074167	0.00000396	0.000746457	1	1.23984E-05	0.00322459
ILMN_2447538	2210018M11RIK	1.10801562	0.0006399	0.0211535	0.0006399	0.01941092	0.0000305	0.00278714	0.0000653	0.005121772	1	0.000306263	0.02048222
ILMN_1222917	PTPN1	1.107980121	0.0032539	0.05678214	0.00373333	0.05925673	0.00204418	0.04892042	0.00362761	0.068031509	0	0.007351981	0.11667667
ILMN_1255086	2810454F19RIK	1.107686745	0.0067415	0.08943186	0.00651414	0.08446632	0.00242497	0.05418861	0.00487539	0.080587642	0	0.007351739	0.11667667
ILMN_1233554	PBRM1	1.107679536	0.00149689	0.03478153	0.00094262	0.02430167	0.00059016	0.02253483	0.00040478	0.01751061	1	0.000844832	0.03651291
ILMN_1234072	PDLIM1	1.107488297	0.0002995	0.01489206	0.0002995	0.01335371	0.0000459	0.00372562	0.0000726	0.005551592	1	0.000306263	0.02048222
ILMN_1216561	CAMK2D	1.107443275	0.00122569	0.03054155	0.00094262	0.02430167	0.00076398	0.02667747	0.00134692	0.037363102	1	0.00305523	0.07341857
ILMN_2590638	BCL2L11	1.107365706	0.00122569	0.03054155	0.00122569	0.02881591	0.0000915	0.00623516	0.0000482	0.004197605	1	0.000176289	0.01444673
ILMN_2705878	LIMD2	1.107359113	0.0002995	0.01489206	0.0002995	0.01335371	0.00000896	0.00116209	0.00000904	0.001335714	1	6.22097E-05	0.00789013
ILMN_1227100	E130112E08RIK	1.107230432	0.0020184	0.04200694	0.00276802	0.04845153	0.00208027	0.04952957	0.00135255	0.037429791	1	0.00040803	0.02413289
ILMN_1254814	CLK1	1.10722634	0.00094262	0.02607154	0.00094262	0.02430167	0.00022953	0.01197773	0.00041438	0.017763501	1	0.00099928	0.0402366
ILMN_2986458	TERF2IP	1.107174717	0.0002995	0.01489206	0.0002995	0.01335371	0.00036565	0.01644438	0.00025266	0.013009278	1	0.000470028	0.02607676
ILMN_1239729	KIF1B	1.106854993	0.0006399	0.0211535	0.0006399	0.01941092	0.00137718	0.03773799	0.00099268	0.031178183	1	0.000504223	0.02732257
ILMN_1217480	LOC100046080	1.106833133	0.00696781	0.09115463	0.00490758	0.07073729	0.00117721	0.03450589	0.00170887	0.042787906	0	0.004379328	0.09051712
ILMN_2652857	IFI47	1.106721599	0.00943231	0.10825947	0.0076447	0.09407685	0.0082845	0.10948849	0.00387692	0.070436711	0	0.006383169	0.10923805
ILMN_1257107	LOC100043821	1.106674621	0.0006399	0.0211535	0.0006399	0.01941092	0.00054092	0.02135537	0.00117775	0.034456682	1	0.001179524	0.04378253
ILMN_2636339	IRF9	1.106644992	0.00252097	0.04839275	0.00094262	0.02430167	0.00029795	0.01428302	0.00076743	0.026757653	1	0.00270263	0.06885567
ILMN_2479848	SIF1	1.106503824	0.0002995	0.01489206	0.0002995	0.01335371	3.51E-08	0.0000177	2.82E-07	0.000110081	1	5.89482E-06	0.0021116
ILMN_1226514	GAB3	1.106492684	0.0002995	0.01489206	0.0002995	0.01335371	0.00000136	0.0002775	2.37E-07	0.000101599	1	6.1646E-06	0.0021257
ILMN_3141048	SEPP1	1.106305884	0.00149689	0.03478153	0.00094262	0.02430167	0.00028342	0.01382831	0.0001664	0.009994028	1	0.000643	0.03157309
ILMN_2635871	3110057O12RIK	1.106105831	0.0006399	0.0211535	0.0006399	0.01941092	0.00015081	0.00885986	0.00020499	0.011473406	1	0.000643034	0.03157309
ILMN_2829625	NTNG1	1.106001213	0.00122569	0.03054155	0.00122569	0.02881591	0.00014765	0.00875482	0.00041707	0.017826837	1	0.000438006	0.02507734
ILMN_2635132	FOXP3	1.105736567	0.0006399	0.0211535	0.0002995	0.01335371	0.00000368	0.00061365	0.00000951	0.00136995	1	0.001301631	0.04617913
ILMN_1225109	2310047C21RIK	1.105585656	0.00094262	0.02607154	0.00094262	0.02430167	0.00023145	0.01201016	0.00046395	0.019281568	1	0.000559888	0.02915112
ILMN_1228653	ZBP1	1.105391357	0.00898742	0.10547593	0.00809366	0.09652695	0.00364092	0.06763268	0.00593208	0.089284737	0	0.011706901	0.14779526
ILMN_1236585	LOC634213	1.105197029	0.0032539	0.05678214	0.00149689	0.03284241	0.00010667	0.00697357	0.00036187	0.016337543	0	0.001797898	0.05487657
ILMN_1227803	LOC674707	1.105118227	0.0006399	0.0211535	0.00094262	0.02430167	0.00000863	0.00113739	0.0000456	0.00403955	1	7.28705E-05	0.00865281
ILMN_2706631	LOC100048076	1.105000545	0.0002995	0.01489206	0.0002995	0.01335371	5.68E-07	0.00014379	0.00000114	0.000290477	1	7.68769E-06	0.0024016
ILMN_2949605	UBAC2	1.104949833	0.0002995	0.01489206	0.0002995	0.01335371	4.68E-07	0.00012677	0.00000161	0.000370841	1	7.28705E-05	0.00865281
ILMN_2651054	LOC100047173	1.104947245	0.00122569	0.03054155	0.00094262	0.02430167	0.0001854	0.01012894	0.00020712	0.011559512	1	0.002540648	0.06640064
ILMN_2691192	RBBP7	1.104851088	0.00741953	0.09487807	0.01186014	0.12006629	0.0247443	0.19992306	0.01812994	0.165469515	0	0.013719454	0.16025079
ILMN_2569336	A130024J05RIK	1.104817015	0.00965407	0.11001819	0.01031818	0.11074271	0.00502937	0.08208706	0.00762986	0.10204046	0	0.012022966	0.14955451
ILMN_1222346	A630097D09RIK	1.104807842	0.0002995	0.01489206	0.0002995	0.01335371	0.00000699	0.00098038	0.0000116	0.001590823	1	1.60246E-05	0.00367466
ILMN_1255419	ZFPN1A1	1.10475855	0.00122569	0.03054155	0.00122569	0.02881591	0.00023251	0.01202516	0.00046107	0.019196381	1	0.001633268	0.05224999

ILMN_2704822	ACAA2	1.104751617	0.00227139	0.04545806	0.00227139	0.0429166	0.00073722	0.02599654	0.00150758	0.039781954	1	0.002041151	0.05875662
ILMN_2595967	LOC100039532	1.104726083	0.0002995	0.01489206	0.0002995	0.01335371	0.0000399	0.00337413	0.0000835	0.006132211	1	0.000353719	0.02219068
ILMN_2628174	ACSS1	1.104609544	0.0002995	0.01489206	0.0002995	0.01335371	0.00000673	0.00095405	0.00000329	0.000651535	1	5.51982E-05	0.00760204
ILMN_2457324	TSSC1	1.10460787	0.00094262	0.02607154	0.0006399	0.01941092	0.00037762	0.01683607	0.00068122	0.024908549	1	0.001301631	0.04617913
ILMN_2631994	HEXIM1	1.104522651	0.0002995	0.01489206	0.0002995	0.01335371	7.94E-07	0.00018585	5.26E-07	0.000168884	1	3.28593E-06	0.00154495
ILMN_2544890	PDE4B	1.104516163	0.00276802	0.05133777	0.0032539	0.05432415	0.00144645	0.03905335	0.00467606	0.078680163	0	0.00388914	0.08408165
ILMN_2696491	PHF11	1.104484414	0.00420612	0.06669083	0.00252097	0.04602629	0.00130622	0.0366489	0.00177754	0.04368478	0	0.003888993	0.08408165
ILMN_2775098	CYB5	1.104384533	0.0002995	0.01489206	0.0002995	0.01335371	0.00000016	0.0000542	3.92E-07	0.00013797	1	5.89742E-06	0.0021116
ILMN_2880467	LASS4	1.104325447	0.00227139	0.04545806	0.00176049	0.03635757	0.00059615	0.02265805	0.00077485	0.026955849	1	0.00099928	0.0402366
ILMN_2812244	MPPE1	1.104198108	0.0002995	0.01489206	0.0002995	0.01335371	0.00000576	0.00084519	0.00000933	0.001361621	1	4.33673E-05	0.0065968
ILMN_3133748	GAB3	1.1040901	0.00149689	0.03478153	0.00122569	0.02881591	0.000026	0.00247667	0.0001002	0.00697141	1	0.000600122	0.03046224
ILMN_2518828	ZNF24	1.104037027	0.0006399	0.0211535	0.0002995	0.01335371	0.0000988	0.00658207	0.00018603	0.010797146	1	0.00011618	0.0112429
ILMN_1258965	TMEM66	1.10397338	0.00094262	0.02607154	0.00094262	0.02430167	0.00012203	0.00760514	0.00027116	0.013615504	1	0.0007895	0.03543767
ILMN_1237886	ENC1	1.103956093	0.0006399	0.0211535	0.0002995	0.01335371	0.0000265	0.00250371	0.0000379	0.003587283	1	0.000135361	0.01242731
ILMN_2492102	LOC630408	1.103768241	0.0006399	0.0211535	0.0002995	0.01335371	0.00021339	0.0113638	0.00034026	0.015806312	1	0.000966442	0.03935694
ILMN_2710166	DDX3X	1.103764891	0.0051392	0.07619761	0.00467484	0.06877491	0.00321609	0.06358903	0.00370058	0.068707988	0	0.004510321	0.09155774
ILMN_2742928	FXYD5	1.103662574	0.0198742	0.16408427	0.01491383	0.13744404	0.00597998	0.09087506	0.00889638	0.111496961	0	0.013017012	0.15603988
ILMN_3071525	CD226	1.103645914	0.00349473	0.05908105	0.0020184	0.03953445	0.00073613	0.02597776	0.00079434	0.027327392	0	0.001977658	0.05767797
ILMN_2720820	A230046K03RIK	1.103616266	0.0002995	0.01489206	0.0002995	0.01335371	0.00000291	0.00051317	0.0000077	0.001222667	1	8.19763E-05	0.00930671
ILMN_1238069	4930539E08RIK	1.103535154	0.0002995	0.01489206	0.0002995	0.01335371	0.0000032	0.00055228	0.0000217	0.002508955	1	0.000157497	0.01350097
ILMN_1238285	DCUN1D5	1.103527312	0.00149689	0.03478153	0.00149689	0.03284241	0.00034811	0.01594848	0.00028909	0.014164441	1	0.000284812	0.01943975
ILMN_1234133	3632431M01RIK	1.103406406	0.00094262	0.02607154	0.0006399	0.01941092	0.00032	0.01501554	0.00049525	0.020203747	1	0.000284828	0.01943975
ILMN_1217705	C130002K18RIK	1.103274712	0.00831809	0.10165638	0.01031818	0.11074271	0.00823865	0.10909937	0.01077307	0.124430321	0	0.015225452	0.168939
ILMN_2614966	RAB27A	1.103217796	0.0002995	0.01489206	0.0002995	0.01335371	8.05E-08	0.0000329	2.31E-08	0.0000187	1	1.2393E-06	0.00090134
ILMN_1245393	STXBP3	1.103174614	0.00397039	0.064249	0.00227139	0.0429166	0.0011527	0.03421849	0.00190089	0.045691414	0	0.00553098	0.10148188
ILMN_1239726	SNAI3	1.103168493	0.0006399	0.0211535	0.0006399	0.01941092	0.0000322	0.00289276	0.00011372	0.007705253	1	0.000665544	0.03206944
ILMN_1223028	D230020C06RIK	1.103101789	0.0006399	0.0211535	0.0006399	0.01941092	0.00028646	0.01388928	0.00034886	0.016068328	1	0.000873828	0.03714525
ILMN_2854878	NECAP1	1.10302603	0.0002995	0.01489206	0.0002995	0.01335371	0.00000877	0.00114799	0.0000229	0.002603706	1	8.19763E-05	0.00930671
ILMN_1242802	RAB6	1.103017062	0.00094262	0.02607154	0.0006399	0.01941092	0.00061393	0.02295322	0.00031887	0.015112162	1	0.001856078	0.05577459
ILMN_2535779	LOC383706	1.102993315	0.0006399	0.0211535	0.00094262	0.02430167	0.00056898	0.02197867	0.00070261	0.025381142	1	0.001104095	0.04229821
ILMN_1228235	CTSE	1.102982206	0.00094262	0.02607154	0.00094262	0.02430167	0.00029079	0.01407	0.00018402	0.010707081	1	0.00057968	0.02968357
ILMN_3163163	A430078G23RIK	1.102898707	0.0006399	0.0211535	0.0006399	0.01941092	0.00013728	0.00835294	0.00013654	0.008839388	1	0.00022037	0.01646479
ILMN_2732190	PBRM1	1.102890972	0.00605844	0.08369461	0.00397039	0.06196763	0.00114065	0.03401276	0.00113476	0.033772175	0	0.013719454	0.16025079
ILMN_1246770	YBX3	1.102889488	0.00349473	0.05908105	0.00301234	0.05155233	0.00358474	0.06731425	0.00316517	0.062746493	0	0.005858095	0.10440833
ILMN_1250135	A930005H10RIK	1.102857125	0.0006399	0.0211535	0.0006399	0.01941092	0.0000434	0.00359485	0.0000827	0.006091257	1	0.000329201	0.02128238
ILMN_3114641	PIK3R1	1.102785193	0.0002995	0.01489206	0.0002995	0.01335371	0.00000126	0.00026389	0.00000119	0.00029799	1	1.47177E-05	0.00353126
ILMN_2677056	LOC100048622	1.102768087	0.0020184	0.04200694	0.0020184	0.03953445	0.00246416	0.05479494	0.00260119	0.055447887	0	0.003774648	0.08295494
ILMN_1243042	LOC381214	1.102758352	0.0002995	0.01489206	0.0002995	0.01335371	0.00000214	0.0004015	0.0000184	0.002263583	1	4.33673E-05	0.0065968
ILMN_2917338	RNF125	1.102623511	0.00373333	0.06184411	0.0032539	0.05432415	0.00210043	0.0498312	0.00339438	0.065464235	0	0.00270263	0.06885567
ILMN_2433964	GIGYF1	1.102596985	0.00176049	0.0385938	0.00149689	0.03284241	0.00047117	0.01946027	0.00035965	0.0162751	1	0.00057968	0.02968357
ILMN_2566477	C730026O12RIK	1.102585731	0.00854165	0.10305721	0.01076004	0.11338366	0.00953803	0.11842272	0.01173891	0.130774947	0	0.012346572	0.15195555
ILMN_2704823	ACAA2	1.102584401	0.00176049	0.0385938	0.00122569	0.02881591	0.00099103	0.03127428	0.00059447	0.022718354	1	0.001104095	0.04229821
ILMN_1249863	SLAMF1	1.102358687	0.00149689	0.03478153	0.00094262	0.02430167	0.00053162	0.02111665	0.00018539	0.010773166	1	0.001686537	0.05325863
ILMN_2617820	PPP3CC	1.10232076	0.0002995	0.01489206	0.0002995	0.01335371	5.55E-07	0.00014264	7.19E-07	0.000216047	1	1.47177E-05	0.00353126
ILMN_1238109	PP11R	1.102299387	0.0002995	0.01489206	0.0002995	0.01335371	0.00010362	0.00682223	0.0000106	0.001483462	1	3.68613E-05	0.00599924
ILMN_1257463	BCL11A	1.102238843	0.00094262	0.02607154	0.00094262	0.02430167	0.00064732	0.02378135	0.00029644	0.014423405	1	0.001531347	0.05016159
ILMN_2634157	ZFP654	1.102206279	0.0002995	0.01489206	0.0002995	0.01335371	0.00000507	0.00076441	0.0000188	0.002298746	1	3.12891E-05	0.00543437

ILMN_1238869	LOC278666	1.102138175	0.00467484	0.07150478	0.00276802	0.04845153	0.0006377	0.02359297	0.00121677	0.035196389	0	0.00305523	0.07341857
ILMN_1215910	FOXN2	1.102070233	0.0002995	0.01489206	0.0002995	0.01335371	0.00074588	0.02612373	0.00053798	0.021230722	1	0.000438006	0.02507734
ILMN_2621086	FLI1	1.102009965	0.00122569	0.03054155	0.00149689	0.03284241	0.00147107	0.03946627	0.00070355	0.025381142	1	0.000873828	0.03714525
ILMN_2699531	RGS10	1.101989172	0.00227139	0.04545806	0.00149689	0.03284241	0.00051989	0.02080755	0.00041221	0.017749337	1	0.001068077	0.04167292
ILMN_2603187	MECP2	1.101917508	0.0002995	0.01489206	0.0002995	0.01335371	0.00000123	0.00026043	0.00000145	0.000347545	1	5.39498E-06	0.00202516
ILMN_2982781	KCNK5	1.101765886	0.0006399	0.0211535	0.0006399	0.01941092	0.0000223	0.00222523	0.0000282	0.002959627	1	0.000151664	0.01324485
ILMN_1244845	NARF	1.101738476	0.00094262	0.02607154	0.00094262	0.02430167	0.0000508	0.00397491	0.00015962	0.00973796	1	0.000453754	0.02560106
ILMN_2680398	ZC3H12D	1.10146721	0.0002995	0.01489206	0.0002995	0.01335371	0.000001	0.00021909	9.52E-07	0.000257701	1	7.03927E-06	0.00230764
ILMN_2605031	E330018D03RIK	1.101463118	0.0056004	0.08017457	0.00831809	0.09800443	0.00453712	0.07707642	0.01264569	0.136133148	0	0.010802479	0.14220108
ILMN_2617477	8030476J24	1.101261776	0.00122569	0.03054155	0.00122569	0.02881591	0.00015789	0.00910673	0.00017366	0.010310561	1	0.00010758	0.01083883
ILMN_2901284	ADD3	1.101189602	0.0002995	0.01489206	0.0002995	0.01335371	0.0000471	0.00380085	0.0000359	0.003445285	1	4.70154E-05	0.00688184
ILMN_2506499	UBE3A	1.101180473	0.00252097	0.04839275	0.00252097	0.04602629	0.00053169	0.02111665	0.00192593	0.046019516	1	0.004924874	0.09535694
ILMN_2605960	RAB19	1.101133403	0.0020184	0.04200694	0.00149689	0.03284241	0.00042802	0.01837561	0.00058953	0.022608846	1	0.001141234	0.04287409
ILMN_2562725	C730013O11RIK	1.101075632	0.00094262	0.02607154	0.00094262	0.02430167	0.00087707	0.02868922	0.00102151	0.031783537	1	0.000504223	0.02732257
ILMN_2567626	PUM1	1.101065176	0.00628646	0.08573635	0.0056004	0.0767776	0.00642098	0.09434264	0.0045757	0.077674245	0	0.012677869	0.1539569
ILMN_2954868	OASL2	1.101052773	0.00227139	0.04545806	0.00301234	0.05155233	0.00495144	0.08123106	0.00212755	0.048753581	0	0.0010331	0.04099743
ILMN_1233894	DTNB	1.100978861	0.0002995	0.01489206	0.0002995	0.01335371	0.00039474	0.01735374	0.00100272	0.0313667	1	0.00057968	0.02968357
ILMN_1229245	INPP4B	1.100970899	0.00227139	0.04545806	0.00176049	0.03635757	0.0004464	0.01884113	0.00062485	0.023550381	1	0.000873828	0.03714525
ILMN_1256639	CD247	1.100911079	0.0006399	0.0211535	0.0002995	0.01335371	0.0000315	0.0028568	0.0000379	0.003587283	1	0.000353739	0.02219068
ILMN_2631192	VPS26B	1.100779486	0.00467484	0.07150478	0.00227139	0.0429166	0.00243729	0.05437251	0.00115122	0.03404972	0	0.006029251	0.10646569
ILMN_2038768	control_ILMN_203	1.1007468	0.10926429	0.40116694	0.10721317	0.39734945	0.11759807	0.4332967	0.11009287	0.413665062	0	0.246250128	0.60756362
ILMN_2668977	1500032D16RIK	1.100684878	0.0002995	0.01489206	0.0002995	0.01335371	0.00000386	0.00063236	0.00000566	0.00097714	1	1.1877E-05	0.00314139
ILMN_1248211	SIDT1	1.100585537	0.00301234	0.05440113	0.0020184	0.03953445	0.00115892	0.03427199	0.00160715	0.041193921	0	0.002873882	0.07130914
ILMN_2534151	IRGB10	1.100553681	0.00537037	0.07818332	0.00628646	0.0826602	0.03005319	0.22151796	0.00905543	0.112610992	0	0.007994557	0.1216087
ILMN_1224211	EPB4.1L2	1.100521767	0.0051392	0.07619761	0.00696781	0.08825299	0.00796439	0.10708222	0.01547157	0.152284836	0	0.023367993	0.21022612
ILMN_2771182	H2-Q8	1.100477595	0.00252097	0.04839275	0.00176049	0.03635757	0.00048225	0.01977742	0.00025467	0.01309856	1	0.003246828	0.07602117
ILMN_2890357	2610027C15RIK	1.10037148	0.0006399	0.0211535	0.0006399	0.01941092	0.00044866	0.01889928	0.00040132	0.017418469	1	0.000559888	0.02915112
ILMN_2705732	INADL	1.100280563	0.00094262	0.02607154	0.00122569	0.02881591	0.00026059	0.01305657	0.00022306	0.012129499	1	0.000559888	0.02915112
ILMN_2422023	C330006D17RIK	1.10024538	0.00397039	0.064249	0.0051392	0.07282894	0.00529378	0.08485181	0.00649293	0.093577166	0	0.007351981	0.11667667
ILMN_1239398	LOC100046817	1.100205887	0.02094553	0.16993323	0.02372203	0.17961616	0.01005217	0.12237853	0.02557207	0.198492675	0	0.044021446	0.28499962
ILMN_1256245	RLF	1.100181996	0.00537037	0.07818332	0.00786961	0.09521779	0.00363532	0.06760424	0.00863224	0.109699863	0	0.005373592	0.10008988
ILMN_1243846	NRF1	1.100170193	0.00122569	0.03054155	0.00149689	0.03284241	0.00073562	0.02597776	0.00238171	0.052317743	0	0.001633268	0.05224999
ILMN_1242769	AKAP8L	1.100071536	0.00349473	0.05908105	0.00349473	0.0566205	0.00184551	0.04588832	0.0029622	0.060255548	0	0.002387591	0.06387081
ILMN_2993109	DDIT4	1.100038813	0.0002995	0.01489206	0.0002995	0.01335371	0.00000961	0.00121195	0.000042	0.003865058	1	0.000146035	0.01292295
ILMN_1245987	HNRNPK	1.100037736	0.01965954	0.16292455	0.0283949	0.19737141	0.02738494	0.21092553	0.04211374	0.257862175	0	0.051397104	0.30742496
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ILMN_2728118	RRP12	-1.100673522	0.0002995	0.01489206	0.0002995	0.01335371	0.0000058	0.00084519	0.00000976	0.001398167	1	2.34093E-05	0.00450296
ILMN_1235470	HNRNPC	-1.100796556	0.0002995	0.01489206	0.0002995	0.01335371	2.8E-08	0.0000148	1.42E-07	0.0000709	1	4.50906E-06	0.00180983
ILMN_2774410	STFA1	-1.100797564	0.0336756	0.21913659	0.03956153	0.23673264	0.03507069	0.2404769	0.03975572	0.250087018	0	0.058515334	0.32634954
ILMN_2856095	ZC3H12A	-1.101004577	0.00149689	0.03478153	0.00094262	0.02430167	0.00016088	0.00919959	0.00033043	0.015473218	1	0.001259689	0.04555924
ILMN_2985447	CMTM7	-1.101081672	0.00094262	0.02607154	0.00094262	0.02430167	0.00036007	0.01627185	0.00030875	0.014785413	1	0.000438006	0.02507734
ILMN_2870487	CPNE2	-1.101235208	0.00301234	0.05440113	0.00176049	0.03635757	0.00015688	0.0090601	0.00033839	0.015735209	0	0.002173782	0.0607706
ILMN_2736762	IFRD2	-1.101280587	0.00943231	0.10825947	0.00898742	0.10212898	0.00427352	0.07427913	0.00677904	0.095608851	0	0.021171123	0.19968637
ILMN_2620061	TBCB	-1.101312875	0.0002995	0.01489206	0.0002995	0.01335371	0.0000296	0.00274031	0.0000316	0.003180587	1	9.5799E-05	0.01018072
ILMN_1252016	ABHD2	-1.101327755	0.00176049	0.0385938	0.0006399	0.01941092	0.0000452	0.003705	0.00013411	0.00874694	1	0.000453754	0.02560106
ILMN_2683802	NUDT9	-1.101534614	0.0002995	0.01489206	0.0002995	0.01335371	0.00000633	0.00091523	0.0000127	0.001692242	1	7.57938E-05	0.00879794
ILMN_2758087	CCNT1	-1.101561438	0.00349473	0.05908105	0.0032539	0.05432415	0.00117117	0.034443	0.00137359	0.03783222	0	0.003663228	0.08166297
ILMN_1222246	ADFP	-1.101682242	0.00943231	0.10825947	0.00854165	0.09937884	0.00289096	0.0601428	0.00520412	0.083438223	0	0.013017012	0.15603988
ILMN_1250149	DNMT3L	-1.101692032	0.00094262	0.02607154	0.0002995	0.01335371	0.0000385	0.00328743	0.000081	0.006004936	1	0.000135361	0.01242731
ILMN_2855423	UBE3B	-1.101823534	0.00467484	0.07150478	0.00444101	0.06659434	0.00097578	0.0310015	0.00261887	0.055581773	0	0.011096803	0.14428014
ILMN_3093150	NPM3	-1.101881244	0.01076004	0.11696153	0.01207886	0.12146481	0.00748853	0.10343287	0.01078041	0.12447925	0	0.018679697	0.18694557
ILMN_2887208	RAB1B	-1.1018898	0.00741953	0.09487807	0.00467484	0.06877491	0.00211426	0.04998366	0.00162135	0.041443788	0	0.005220076	0.09861156
ILMN_1246622	9130204C11RIK	-1.102206651	0.00094262	0.02607154	0.0006399	0.01941092	0.0000832	0.0058247	0.0000636	0.005055758	1	0.000246108	0.01770572
ILMN_1237507	DLST	-1.102242835	0.0002995	0.01489206	0.0002995	0.01335371	0.0000239	0.0023395	0.0000261	0.002837023	1	4.70154E-05	0.00688184
ILMN_2615739	GM459	-1.102378757	0.01750895	0.15321051	0.0211598	0.1686674	0.01902429	0.17493554	0.02815215	0.207735874	0	0.018679697	0.18694557
ILMN_2605767	REPIN1	-1.102407679	0.0002995	0.01489206	0.0002995	0.01335371	0.00047865	0.01968165	0.0000565	0.004637506	1	0.000120719	0.01149104
ILMN_2675033	SLC9A7	-1.102560823	0.0002995	0.01489206	0.0002995	0.01335371	0.0000189	0.00194817	0.0000376	0.003576126	1	9.5799E-05	0.01018072
ILMN_2531520	GM962	-1.10277933	0.0006399	0.0211535	0.0006399	0.01941092	0.0000441	0.00363684	0.0000899	0.006457872	1	0.000393771	0.02371136
ILMN_2952587	INTS5	-1.102916647	0.01469649	0.13944707	0.01273594	0.12533842	0.00646817	0.09479661	0.00750925	0.101343301	0	0.008450429	0.12538799
ILMN_3162081	WDR6	-1.103000504	0.00149689	0.03478153	0.0020184	0.03953445	0.00047402	0.01954308	0.00088629	0.029245777	1	0.000934606	0.03863507
ILMN_2823778	SC4MOL	-1.103118657	0.00094262	0.02607154	0.0002995	0.01335371	0.00060963	0.02290284	0.00035368	0.016129651	1	0.000176289	0.01444673
ILMN_2637804	4933407P14RIK	-1.103123645	0.02775949	0.19711952	0.02881875	0.19934791	0.03335811	0.23451441	0.02708149	0.204795156	0	0.03192796	0.24475474
ILMN_2944939	CAMK1	-1.103291951	0.0002995	0.01489206	0.0002995	0.01335371	0.0000298	0.00274909	0.0000185	0.002263791	1	3.12891E-05	0.00543437
ILMN_2966386	RCL1	-1.10330649	0.0006399	0.0211535	0.0006399	0.01941092	0.00000151	0.00030356	0.00000531	0.000929895	1	8.86216E-05	0.00982291
ILMN_2721208	MSTO1	-1.103313852	0.0076447	0.09672601	0.0051392	0.07282894	0.00087596	0.02868922	0.00154119	0.04014427	0	0.005531174	0.10148188
ILMN_1243107	CENTD3	-1.103383796	0.0006399	0.0211535	0.0006399	0.01941092	0.0000139	0.00158406	0.0000239	0.002688276	1	0.000204639	0.01592867
ILMN_2491232	USP36	-1.103389463	0.0020184	0.04200694	0.00149689	0.03284241	0.00016003	0.00916202	0.00017844	0.010486465	1	0.003055109	0.07341857
ILMN_1259100	PILRB1	-1.103436708	0.00490758	0.07399298	0.00301234	0.05155233	0.00088463	0.0288961	0.0019523	0.046411523	0	0.002173782	0.0607706
ILMN_1225747	ZNFN1A3	-1.103489414	0.0002995	0.01489206	0.0002995	0.01335371	0.0000072	0.00099242	0.0000278	0.002931426	1	0.000453754	0.02560106
ILMN_2721149	ARL11	-1.103567882	0.0032539	0.05678214	0.00349473	0.0566205	0.00078155	0.02696727	0.00091667	0.029754618	0	0.002620495	0.06768933
ILMN_1244424	ADORA2B	-1.103675196	0.00420612	0.06669083	0.00252097	0.04602629	0.00070446	0.02533145	0.00066071	0.024405921	0	0.00388914	0.08408165
ILMN_1228832	NGP	-1.103786521	0.01295435	0.12973001	0.01076004	0.11338366	0.00414593	0.07330247	0.00400122	0.071825953	0	0.011398229	0.14607747
ILMN_1260456	HSD3B7	-1.103805679	0.0002995	0.01489206	0.0002995	0.01335371	8.64E-07	0.00019904	0.00000221	0.000472255	1	2.15311E-05	0.0043202
ILMN_1227235	TIMM10	-1.103984846	0.00122569	0.03054155	0.00122569	0.02881591	0.0003537	0.01612517	0.0005671	0.0219992	1	0.000763113	0.03482416
ILMN_2871749	EAR6	-1.10402136	0.0032539	0.05678214	0.00490758	0.07073729	0.00962513	0.11918617	0.00641492	0.093049294	0	0.005220076	0.09861156
ILMN_2911344	PLSCR1	-1.104115255	0.0002995	0.01489206	0.0002995	0.01335371	0.00055175	0.02156346	0.00011527	0.007776142	1	0.000329201	0.02128238
ILMN_2698494	NFU1	-1.104319371	0.00122569	0.03054155	0.00122569	0.02881591	0.00101187	0.03167407	0.00130944	0.036673066	1	0.001301631	0.04617913
ILMN_2603898	CLEC4B1	-1.104355951	0.00149689	0.03478153	0.0006399	0.01941092	0.00047724	0.01964113	0.00013919	0.008973291	1	0.00042277	0.02466001
ILMN_2749448	PLEKHO2	-1.104536512	0.00149689	0.03478153	0.00149689	0.03284241	0.0000583	0.00441806	0.00017802	0.010475755	1	0.000600091	0.03046224
ILMN_2631014	PIAS3	-1.104655312	0.0002995	0.01489206	0.0002995	0.01335371	0.00000858	0.00113395	0.0000309	0.003134864	1	3.39668E-05	0.00570777
ILMN_2595863	CHST10	-1.10468852	0.0002995	0.01489206	0.0002995	0.01335371	0.00011639	0.00743132	0.00030356	0.01463008	1	0.00022037	0.01646479
ILMN_1231439	AATK	-1.104893386	0.00227139	0.04545806	0.00149689	0.03284241	0.0000541	0.00416529	0.00025931	0.013278569	1	0.003449313	0.07881943
ILMN_2923607	PHLDA3	-1.105141716	0.0006399	0.0211535	0.0002995	0.01335371	0.0000359	0.00314503	0.0000324	0.003223303	1	5.09531E-05	0.00725295

ILMN_2544343	STAB1	-1.105676499	0.0002995	0.01489206	0.0002995	0.01335371	0.00000574	0.00084519	0.0000233	0.002627969	1	0.000176289	0.01444673
ILMN_1238102	IDE	-1.105690099	0.04959771	0.27047142	0.05750633	0.289534	0.03780343	0.24938156	0.06636787	0.321827801	0	0.059776798	0.32882056
ILMN_2834198	SCN1B	-1.106256844	0.0002995	0.01489206	0.0006399	0.01941092	0.00023767	0.01217572	0.00044649	0.018790822	1	0.000453754	0.02560106
ILMN_1236702	LILRB4	-1.10637923	0.01076004	0.11696153	0.00898742	0.10212898	0.00224068	0.05176032	0.00387533	0.070435395	0	0.017311316	0.18018556
ILMN_2979639	H2-DMB2	-1.106407472	0.00227139	0.04545806	0.0020184	0.03953445	0.00172654	0.04391533	0.00099673	0.031258932	1	0.00270263	0.06885567
ILMN_1256817	SLPI	-1.106517473	0.04395927	0.25213143	0.03008794	0.20371558	0.01322187	0.14325168	0.01654123	0.157798872	0	0.038432634	0.26812964
ILMN_2590350	UBE2F	-1.106602174	0.00094262	0.02607154	0.00094262	0.02430167	0.00030653	0.0145343	0.000065	0.005110515	1	0.000157497	0.01350097
ILMN_1240318	SLC7A7	-1.106705276	0.0002995	0.01489206	0.0002995	0.01335371	0.00037337	0.01669711	0.0005249	0.020878705	1	0.000470028	0.02607676
ILMN_1215893	ALG3	-1.106724214	0.0002995	0.01489206	0.0002995	0.01335371	0.00000791	0.00106049	0.00000859	0.001299233	1	0.000212368	0.01604723
ILMN_2780915	PRMT7	-1.106850835	0.00149689	0.03478153	0.00122569	0.02881591	0.00043663	0.01861404	0.0006752	0.024769672	1	0.002387492	0.06387081
ILMN_2746830	BC022224	-1.106855817	0.00397039	0.064249	0.0020184	0.03953445	0.00012205	0.00760514	0.000874	0.02899696	0	0.005858907	0.10440833
ILMN_3120014	SRI	-1.106861448	0.00876432	0.1043511	0.01053919	0.11232356	0.01267052	0.13982328	0.01322195	0.139651023	0	0.029744406	0.23776625
ILMN_2959292	UPP1	-1.107047972	0.0067415	0.08943186	0.00831809	0.09800443	0.00616669	0.09223153	0.00737179	0.100219589	0	0.008450429	0.12538799
ILMN_2633457	1110057K04RIK	-1.107066336	0.0006399	0.0211535	0.0006399	0.01941092	0.0002621	0.01311825	0.00018047	0.010552902	1	0.000688785	0.03268184
ILMN_2646209	CDK10	-1.107106695	0.01164003	0.12184595	0.00965407	0.10652405	0.00837294	0.10993164	0.00597071	0.089478328	0	0.004644853	0.0931111
ILMN_2680440	ATP6V1B2	-1.107126066	0.00122569	0.03054155	0.00094262	0.02430167	0.0000173	0.00183184	0.00015479	0.009492492	1	0.00057965	0.02968357
ILMN_2691706	SAC3D1	-1.107157088	0.00227139	0.04545806	0.0020184	0.03953445	0.00059451	0.02265805	0.00187868	0.045262385	1	0.001531347	0.05016159
ILMN_1241909	ATL3	-1.107229662	0.00176049	0.0385938	0.0002995	0.01335371	0.0001247	0.00774952	0.0002357	0.012495554	1	0.001301631	0.04617913
ILMN_2686975	FAM129B	-1.107251043	0.00094262	0.02607154	0.0006399	0.01941092	0.00010016	0.00665043	0.0000642	0.005083088	1	0.000621233	0.03109305
ILMN_2900557	KIF15	-1.107418991	0.0056004	0.08017457	0.00252097	0.04602629	0.00050815	0.02053213	0.00073746	0.02616347	0	0.002314175	0.06295874
ILMN_2745954	1110007L15RIK	-1.107513874	0.0006399	0.0211535	0.0002995	0.01335371	0.00025743	0.01295401	0.00026747	0.013561762	1	0.000284828	0.01943975
ILMN_1226372	RFFL	-1.107562515	0.00094262	0.02607154	0.0006399	0.01941092	0.0000159	0.00174469	0.000055	0.004568149	1	0.000379979	0.02324165
ILMN_3084818	NR2C2AP	-1.107652217	0.00227139	0.04545806	0.00122569	0.02881591	0.00042107	0.01819815	0.00097889	0.030933174	1	0.001797898	0.05487657
ILMN_1248733	PA2G4	-1.107667438	0.00176049	0.0385938	0.00252097	0.04602629	0.00225915	0.05195492	0.0039532	0.071295686	0	0.002787111	0.07008733
ILMN_2630605	FSCN1	-1.107768152	0.00809366	0.10014632	0.00605844	0.08075955	0.0018293	0.04560708	0.00255619	0.054799056	0	0.007351981	0.11667667
ILMN_3003631	PPAP2C	-1.10780952	0.00276802	0.05133777	0.00276802	0.04845153	0.00099443	0.03132914	0.00125441	0.035750241	0	0.000934606	0.03863507
ILMN_2598775	STARD3NL	-1.107943892	0.00176049	0.0385938	0.00149689	0.03284241	0.0000601	0.00452448	0.00015332	0.009469751	1	0.000737547	0.0342621
ILMN_2588995	RAB8B	-1.108140051	0.00467484	0.07150478	0.0020184	0.03953445	0.00061097	0.02292456	0.00068182	0.024911182	0	0.00099904	0.0402366
ILMN_2936468	5730596K20RIK	-1.108252625	0.0002995	0.01489206	0.0002995	0.01335371	8.48E-07	0.00019639	0.00000286	0.000576709	1	3.26018E-05	0.00557911
ILMN_2699522	DYRK3	-1.108291839	0.0002995	0.01489206	0.0002995	0.01335371	0.0000346	0.00306253	0.0000326	0.003233591	1	2.65234E-05	0.00480383
ILMN_2611431	PPP3CA	-1.108544093	0.01901516	0.15981086	0.02308219	0.177055	0.0308581	0.22442614	0.03082622	0.218815938	0	0.043046488	0.28193118
ILMN_2908056	TMBIM1	-1.108696543	0.0002995	0.01489206	0.0002995	0.01335371	0.00035559	0.01617837	0.00070271	0.025381142	1	0.000844832	0.03651291
ILMN_2744909	GMPPB	-1.108708169	0.0006399	0.0211535	0.0006399	0.01941092	0.00218189	0.05098423	0.00160119	0.041131766	0	0.001218998	0.0445025
ILMN_2925281	ABCD3	-1.108715146	0.0002995	0.01489206	0.0002995	0.01335371	1.43E-07	0.0000497	1.83E-07	0.0000833	1	1.89069E-06	0.00111411
ILMN_2988931	STFA1	-1.108889714	0.01426212	0.13687557	0.01621381	0.14443088	0.0128175	0.14064502	0.01425719	0.145852642	0	0.022800994	0.20757243
ILMN_2819679	TMEM50A	-1.108893575	0.01664564	0.14895372	0.01858605	0.1562833	0.01881688	0.17402897	0.01897851	0.169539906	0	0.032684998	0.24738569
ILMN_2698430	BCL2L1	-1.109012645	0.00094262	0.02607154	0.00094262	0.02430167	0.00084298	0.02806722	0.00013557	0.008801061	1	0.000621233	0.03109305
ILMN_3137980	ZFP41	-1.109014707	0.0002995	0.01489206	0.0002995	0.01335371	0.0000051	0.00076551	0.00000777	0.001225434	1	3.25994E-05	0.00557911
ILMN_2914507	NDUFB6	-1.109148444	0.00628646	0.08573635	0.00628646	0.0826602	0.00323475	0.06374761	0.00475793	0.079602307	0	0.007994557	0.1216087
ILMN_1243329	DAB2	-1.109426935	0.01186014	0.12340942	0.00809366	0.09652695	0.0024452	0.05450994	0.00311624	0.062120568	0	0.029045675	0.23488344
ILMN_2640453	WDR55	-1.109433931	0.0006399	0.0211535	0.0006399	0.01941092	0.0000894	0.00612683	0.00012054	0.008038629	1	0.000237231	0.01736224
ILMN_2867696	CDC42BPB	-1.110032665	0.0002995	0.01489206	0.0002995	0.01335371	0.0000456	0.00372478	0.0001107	0.007522402	1	0.000379979	0.02324165
ILMN_2795412	TMEM176A	-1.110201644	0.0006399	0.0211535	0.0006399	0.01941092	0.0000316	0.00285855	0.0000256	0.002802168	1	8.86334E-05	0.00982291
ILMN_2727273	SWAP70	-1.110366306	0.0002995	0.01489206	0.0002995	0.01335371	0.00000132	0.00027167	0.0000026	0.000530708	1	2.44059E-05	0.00463717
ILMN_2620767	ABHD2	-1.110517436	0.0002995	0.01489206	0.0002995	0.01335371	0.00000256	0.00046493	0.00000565	0.00097714	1	4.33673E-05	0.0065968
ILMN_1221920	PLEKHG3	-1.110664539	0.0002995	0.01489206	0.0002995	0.01335371	0.0000203	0.00208152	0.0000086	0.001299233	1	1.74444E-05	0.00390377
ILMN_2764607	1810009N02RIK	-1.110668063	0.0002995	0.01489206	0.0002995	0.01335371	0.00000473	0.0007333	0.0000076	0.001211113	1	4.89467E-05	0.00705363

ILMN_2842767	NACC1	-1.110682075	0.0006399	0.0211535	0.0006399	0.01941092	0.00023804	0.01217572	0.00022635	0.012236289	1	0.00042277	0.02466001
ILMN_2755399	PPP2R4	-1.110682315	0.00276802	0.05133777	0.00227139	0.0429166	0.0021293	0.05017441	0.00148083	0.039320129	0	0.001531347	0.05016159
ILMN_1256354	GCLM	-1.110765414	0.00149689	0.03478153	0.00094262	0.02430167	0.0000865	0.00599563	0.0000573	0.004664893	1	7.57938E-05	0.00879794
ILMN_2981689	NUP133	-1.11080026	0.0002995	0.01489206	0.0002995	0.01335371	0.000013	0.00149316	0.00000117	0.000296995	1	7.35697E-06	0.00232956
ILMN_2915303	TREM3	-1.110935528	0.00094262	0.02607154	0.00122569	0.02881591	0.0001306	0.00798826	0.00024248	0.012705581	1	0.000228655	0.01684049
ILMN_1215209	CLECSF9	-1.110943822	0.0198742	0.16408427	0.02030331	0.16494841	0.01231585	0.13728535	0.01456125	0.147630924	0	0.016448649	0.17608907
ILMN_2841290	TNFAIP2	-1.110987512	0.0002995	0.01489206	0.0006399	0.01941092	0.00030838	0.01458748	0.00018794	0.010853565	1	0.000212368	0.01604723
ILMN_2959293	UPP1	-1.111007524	0.00149689	0.03478153	0.00149689	0.03284241	0.00100994	0.03163507	0.00135104	0.037410476	1	0.002314272	0.06295874
ILMN_2614563	APOL7C	-1.111021044	0.0002995	0.01489206	0.0002995	0.01335371	0.0000444	0.00364378	0.00014172	0.009037925	1	0.000237231	0.01736224
ILMN_3160203	ZFP213	-1.11102856	0.0006399	0.0211535	0.0006399	0.01941092	0.0000159	0.00174469	0.0000628	0.00500903	1	0.000306263	0.02048222
ILMN_2601379	MGC18837	-1.111045685	0.0002995	0.01489206	0.0002995	0.01335371	0.0000105	0.00128151	0.0000199	0.002370654	1	4.51564E-05	0.00675851
ILMN_1235000	YIF1A	-1.111117156	0.0006399	0.0211535	0.0006399	0.01941092	0.0000128	0.00148603	0.00000478	0.000855756	1	3.83949E-05	0.00609954
ILMN_2640995	SPIRE2	-1.111127251	0.0002995	0.01489206	0.0002995	0.01335371	1.43E-07	0.0000497	5.59E-07	0.000175929	1	5.39498E-06	0.00202516
ILMN_2884098	GORASP2	-1.111288278	0.0002995	0.01489206	0.0002995	0.01335371	0.00000784	0.00105936	0.0000312	0.003152395	1	7.28705E-05	0.00865281
ILMN_1256142	MARCKS	-1.111356803	0.00537037	0.07818332	0.00176049	0.03635757	0.0000741	0.00534833	0.00026102	0.01332625	0	0.000643034	0.03157309
ILMN_2601147	KDELC1	-1.111368149	0.00176049	0.0385938	0.0020184	0.03953445	0.00053473	0.0212191	0.00078635	0.027233771	1	0.001581552	0.05126497
ILMN_2680549	PIK3CB	-1.111474769	0.0002995	0.01489206	0.0002995	0.01335371	0.00025023	0.01267398	0.00045843	0.01916188	1	0.001686462	0.05325863
ILMN_1218181	IFITM6	-1.111515015	0.00122569	0.03054155	0.00122569	0.02881591	0.00094292	0.03016485	0.00037738	0.0167608	1	0.000643034	0.03157309
ILMN_2550095	6230425C21RIK	-1.111625769	0.00149689	0.03478153	0.00176049	0.03635757	0.00081345	0.02755739	0.00195454	0.046417419	1	0.003149701	0.07483876
ILMN_1224390	1700129I04RIK	-1.111956114	0.0002995	0.01489206	0.0002995	0.01335371	0.00000447	0.00070872	0.0000272	0.002888688	1	0.000189968	0.01508948
ILMN_1240746	MCPT4	-1.111968534	0.00444101	0.0691859	0.00176049	0.03635757	0.0001123	0.0072499	0.00028643	0.014095117	0	0.002173782	0.0607706
ILMN_1230423	SH3PXD2B	-1.111999219	0.0002995	0.01489206	0.0002995	0.01335371	0.0000155	0.00171658	0.00000487	0.000862773	1	7.88278E-05	0.00901523
ILMN_1247468	FTSJ3	-1.112004157	0.0002995	0.01489206	0.0002995	0.01335371	0.0000521	0.00404506	0.0000644	0.005086516	1	6.47271E-05	0.00803428
ILMN_3140913	TBC1D2	-1.112150855	0.0002995	0.01489206	0.0002995	0.01335371	0.0000389	0.00330101	0.00000834	0.001279253	1	0.000111802	0.01097902
ILMN_2519673	VWF	-1.112341924	0.0006399	0.0211535	0.0002995	0.01335371	0.0000321	0.00289074	0.0000414	0.003820132	1	9.21504E-05	0.00995203
ILMN_2617468	CHAC1	-1.112462827	0.00122569	0.03054155	0.00094262	0.02430167	0.00100678	0.03156276	0.00039234	0.017180018	1	0.000665544	0.03206944
ILMN_2450031	SCL0004020.1_31	-1.112588927	0.00094262	0.02607154	0.00094262	0.02430167	0.0000097	0.00121762	0.0000309	0.003134864	1	3.68613E-05	0.00599924
ILMN_2450155	IGLC2_J00595_IG_	-1.112608245	0.0002995	0.01489206	0.0002995	0.01335371	0.00000122	0.00025882	0.0000337	0.003292439	1	0.000317448	0.02078825
ILMN_1218104	5630401D24RIK	-1.112744368	0.0002995	0.01489206	0.0002995	0.01335371	0.00000346	0.00058692	0.00000396	0.000746457	1	5.74504E-05	0.00761864
ILMN_1237743	LOC382813	-1.112766578	0.0002995	0.01489206	0.0002995	0.01335371	6.54E-07	0.0001601	0.00000198	0.000436891	1	1.08955E-05	0.00300091
ILMN_1222872	WBSCR16	-1.112770151	0.00373333	0.06184411	0.00397039	0.06196763	0.00137828	0.03773799	0.00362037	0.068005458	0	0.004924874	0.09535694
ILMN_2687828	ARID3A	-1.112982962	0.00965407	0.11001819	0.00786961	0.09521779	0.00278855	0.05902629	0.00354237	0.067235737	0	0.011096803	0.14428014
ILMN_2772492	TSR1	-1.11339113	0.0002995	0.01489206	0.0002995	0.01335371	0.0000835	0.00583655	0.0000958	0.0067548	1	0.000146035	0.01292295
ILMN_2868480	EAR4	-1.11346403	0.06828805	0.3184975	0.07366518	0.32882749	0.05977412	0.31205079	0.07952314	0.35376248	0	0.035872649	0.25847743
ILMN_1219168	GPN1	-1.113513745	0.0002995	0.01489206	0.0002995	0.01335371	0.00012201	0.00760514	0.00045913	0.01916188	1	0.000621233	0.03109305
ILMN_1214608	PLXND1	-1.113701478	0.00094262	0.02607154	0.0006399	0.01941092	0.0000167	0.00178763	0.0000626	0.00500138	1	0.000816732	0.0360345
ILMN_2723708	FNBP1	-1.113872343	0.0002995	0.01489206	0.0002995	0.01335371	0.00000754	0.00103182	0.0000151	0.001938491	1	5.09531E-05	0.00725295
ILMN_2806180	CSF3R	-1.11399081	0.00176049	0.0385938	0.00149689	0.03284241	0.00012188	0.00760514	0.00034547	0.015942739	1	0.001977658	0.05767797
ILMN_2652172	NAGK	-1.114167208	0.00094262	0.02607154	0.00094262	0.02430167	0.0000386	0.00328743	0.00010625	0.007284834	1	0.000212368	0.01604723
ILMN_2859847	PYGL	-1.114288643	0.00149689	0.03478153	0.00149689	0.03284241	0.00010118	0.00668036	0.0003779	0.0167608	1	0.001482614	0.04961268
ILMN_2470360	BC037704	-1.11448614	0.0002995	0.01489206	0.0002995	0.01335371	0.00000126	0.00026389	0.00000148	0.000354054	1	9.15833E-06	0.00268109
ILMN_1217040	1300001I01RIK	-1.114584244	0.00276802	0.05133777	0.00349473	0.0566205	0.00171808	0.04381888	0.00349757	0.066721909	0	0.005373592	0.10008988
ILMN_1223285	HSPA2	-1.115046275	0.0002995	0.01489206	0.0002995	0.01335371	7.97E-07	0.00018585	0.00000345	0.000677604	1	4.70154E-05	0.00688184
ILMN_2950814	GM962	-1.115047143	0.0067415	0.08943186	0.00537037	0.07497442	0.00081444	0.02757069	0.00231909	0.051476756	0	0.004783009	0.09409752
ILMN_1214952	CLN3	-1.115097709	0.0002995	0.01489206	0.0002995	0.01335371	0.00000672	0.00095405	0.0000454	0.004033989	1	6.73408E-05	0.00831435
ILMN_3163504	METTL4	-1.115151964	0.0002995	0.01489206	0.0002995	0.01335371	0.0000174	0.00183259	0.00000733	0.001185124	1	5.09531E-05	0.00725295
ILMN_2822552	UBTD2	-1.115214016	0.00094262	0.02607154	0.00122569	0.02881591	0.00077456	0.02682534	0.00233485	0.051588335	0	0.00270263	0.06885567

ILMN_2717678	MUC13	-1.115246667	0.0006399	0.0211535	0.0002995	0.01335371	0.00000878	0.00114799	0.0000157	0.00199766	1	5.97852E-05	0.00777325
ILMN_2433547	TRP53BP1	-1.115309394	0.0002995	0.01489206	0.0002995	0.01335371	0.00000111	0.00024093	0.00000369	0.000720943	1	3.53859E-05	0.0058616
ILMN_2788073	HMOX1	-1.115323968	0.00696781	0.09115463	0.00397039	0.06196763	0.00102352	0.0318673	0.00150214	0.039708565	0	0.001977658	0.05767797
ILMN_1219208	NOL6	-1.115717769	0.0002995	0.01489206	0.0002995	0.01335371	0.00000446	0.00070872	0.0000167	0.00209125	1	0.000146035	0.01292295
ILMN_1237430	PHLPP	-1.11586422	0.00122569	0.03054155	0.00122569	0.02881591	0.00024063	0.01226772	0.00035426	0.016129651	1	0.000844832	0.03651291
ILMN_2723483	POLR1B	-1.115874714	0.00122569	0.03054155	0.0006399	0.01941092	0.0000273	0.00256319	0.0000442	0.003965776	1	0.000228655	0.01684049
ILMN_2958484	NLRX1	-1.115901939	0.0006399	0.0211535	0.0006399	0.01941092	0.00000911	0.00116871	0.0000192	0.002327044	1	0.000157497	0.01350097
ILMN_2661367	HYOU1	-1.11593221	0.0006399	0.0211535	0.0006399	0.01941092	0.00036758	0.01649923	0.00030102	0.014549744	1	0.000306263	0.02048222
ILMN_2608145	HDHD3	-1.116104843	0.0002995	0.01489206	0.0002995	0.01335371	0.000037	0.00321551	0.000031	0.003134864	1	0.000228655	0.01684049
ILMN_2791028	APP	-1.116183137	0.00276802	0.05133777	0.00276802	0.04845153	0.00012627	0.00779232	0.00047158	0.019546304	0	0.000540727	0.02850419
ILMN_2524865	CHI3L4	-1.11643408	0.0056004	0.08017457	0.00420612	0.06441203	0.00119938	0.03484851	0.00116094	0.034266489	0	0.012346572	0.15195555
ILMN_1254929	RCL1	-1.116461155	0.0002995	0.01489206	0.0002995	0.01335371	6.64E-07	0.0001602	0.00000774	0.001225133	1	9.21504E-05	0.00995203
ILMN_2939185	BC056474	-1.116523763	0.0002995	0.01489206	0.0002995	0.01335371	0.0000038	0.00063012	0.00000221	0.000472255	1	1.1878E-05	0.00314139
ILMN_1228613	PYCRL	-1.116634512	0.0002995	0.01489206	0.0002995	0.01335371	0.00014129	0.00855208	0.000044	0.003965776	1	5.74504E-05	0.00761864
ILMN_2877507	PIGQ	-1.11667927	0.00094262	0.02607154	0.0006399	0.01941092	0.0000468	0.00378362	0.00015238	0.009444363	1	0.000621233	0.03109305
ILMN_2868131	PIGT	-1.117024219	0.00122569	0.03054155	0.00122569	0.02881591	0.0000929	0.00632166	0.00031205	0.014897503	1	0.0007895	0.03543767
ILMN_1221943	SDF2L1	-1.117198955	0.00301234	0.05440113	0.0020184	0.03953445	0.00040857	0.01777361	0.00080514	0.027596907	0	0.001389407	0.04772897
ILMN_2750515	FOS	-1.11747226	0.0002995	0.01489206	0.0002995	0.01335371	0.0000144	0.00162351	0.000053	0.004480844	1	0.000643034	0.03157309
ILMN_3005873	SORT1	-1.11753372	0.0002995	0.01489206	0.0002995	0.01335371	4.28E-07	0.00011785	5.34E-07	0.000169129	1	3.83949E-05	0.00609954
ILMN_2934448	TJAP1	-1.118088782	0.0002995	0.01489206	0.0002995	0.01335371	0.0000041	0.00066517	0.00000738	0.001188627	1	2.54447E-05	0.00475651
ILMN_1240615	OLFM1	-1.118125635	0.0020184	0.04200694	0.00122569	0.02881591	0.0000124	0.00144846	0.000029	0.003012161	1	0.000284828	0.01943975
ILMN_2706231	SYNGR2	-1.118544974	0.0020184	0.04200694	0.00227139	0.0429166	0.00192157	0.04705068	0.00155324	0.040345167	1	0.00270263	0.06885567
ILMN_2776850	GAS7	-1.118567525	0.0006399	0.0211535	0.0006399	0.01941092	0.0000167	0.00178977	0.0000788	0.005900268	1	0.000140602	0.01273272
ILMN_2815889	GRWD1	-1.118687936	0.0002995	0.01489206	0.0002995	0.01335371	0.0000165	0.00178433	0.0000203	0.002399815	1	3.99889E-05	0.00618393
ILMN_1258394	AARS	-1.118724378	0.0002995	0.01489206	0.0002995	0.01335371	1.52E-08	0.00000944	3.84E-08	0.0000267	1	2.99936E-06	0.00146959
ILMN_2685565	TYMP	-1.119134268	0.0002995	0.01489206	0.0002995	0.01335371	5.95E-07	0.00014895	0.00000154	0.000360893	1	6.47271E-05	0.00803428
ILMN_1249313	RABL3	-1.119280075	0.0002995	0.01489206	0.0002995	0.01335371	0.00000837	0.00111027	0.0000181	0.002239201	1	8.19708E-05	0.00930671
ILMN_2630459	CXCR4	-1.119486645	0.01664564	0.14895372	0.010097	0.10925562	0.00150846	0.04007654	0.00513661	0.082861032	0	0.009432496	0.13248473
ILMN_2736690	2210411K11RIK	-1.119517225	0.0002995	0.01489206	0.0002995	0.01335371	0.00000361	0.00060385	3.36E-07	0.00012714	1	1.64374E-06	0.00107762
ILMN_2987863	PER2	-1.119751625	0.0020184	0.04200694	0.00122569	0.02881591	0.00049047	0.0200248	0.00050945	0.020548879	1	0.001389407	0.04772897
ILMN_2600744	RGS16	-1.119945836	0.0006399	0.0211535	0.0002995	0.01335371	0.0000862	0.00599563	0.0000228	0.002596277	1	5.09531E-05	0.00725295
ILMN_3091641	DAB2	-1.120084423	0.0056004	0.08017457	0.00349473	0.0566205	0.00031561	0.01486932	0.00066486	0.024504648	0	0.003346676	0.07734743
ILMN_2684651	MSI2H	-1.120151943	0.0006399	0.0211535	0.00094262	0.02430167	0.00015616	0.00905564	0.00017757	0.010475755	1	0.00036664	0.02284602
ILMN_2425415	UBE3B	-1.12020859	0.0002995	0.01489206	0.0002995	0.01335371	2.27E-07	0.0000712	3.67E-07	0.000134456	1	2.65234E-05	0.00480383
ILMN_2733733	TLR2	-1.120344381	0.00176049	0.0385938	0.00149689	0.03284241	0.0000662	0.00487536	0.00022244	0.012123944	1	0.000844832	0.03651291
ILMN_2855261	SLC25A39	-1.120465978	0.0002995	0.01489206	0.0002995	0.01335371	0.00020524	0.01103168	0.00039608	0.017311138	1	0.00042277	0.02466001
ILMN_2713464	ABHD4	-1.120638738	0.0002995	0.01489206	0.0002995	0.01335371	0.0000249	0.00241551	0.000033	0.003242217	1	2.76455E-05	0.00493033
ILMN_2574165	SLC7A11	-1.120754955	0.0002995	0.01489206	0.0002995	0.01335371	0.00000981	0.00121884	0.0000519	0.004442214	1	7.0054E-05	0.00846962
ILMN_1259069	F730003H07RIK	-1.121065354	0.02201501	0.1748995	0.01513108	0.13869555	0.00567109	0.08820028	0.00888129	0.111410421	0	0.019156396	0.19024382
ILMN_1252157	A330102K04RIK	-1.121227393	0.0006399	0.0211535	0.0006399	0.01941092	0.0000632	0.00470014	0.0000802	0.005962962	1	0.001179468	0.04378253
ILMN_2935032	FBXL6	-1.121239133	0.0002995	0.01489206	0.0002995	0.01335371	5.04E-07	0.00013181	0.00000874	0.00131658	1	0.000120719	0.01149104
ILMN_1253919	CCL3	-1.121443309	0.00965407	0.11001819	0.00965407	0.10652405	0.00345725	0.06587166	0.00570388	0.08745013	0	0.009432496	0.13248473
ILMN_1260585	STFA2	-1.121655647	0.00094262	0.02607154	0.0006399	0.01941092	0.00017433	0.00971369	0.00029736	0.01443844	1	0.000816732	0.0360345
ILMN_3136638	SNCA	-1.121686063	0.00786961	0.09842737	0.00373333	0.05925673	0.00040521	0.01771	0.00102328	0.031817359	0	0.033458819	0.25026637
ILMN_2936380	SGPL1	-1.121901135	0.0002995	0.01489206	0.0002995	0.01335371	0.0000477	0.00381669	0.0000543	0.004539402	1	6.47271E-05	0.00803428
ILMN_2673211	PFN1	-1.121964524	0.00467484	0.07150478	0.00176049	0.03635757	0.0006747	0.02461215	0.00083935	0.02829048	0	0.005858907	0.10440833
ILMN_1221451	DHRSX	-1.12290417	0.00176049	0.0385938	0.00176049	0.03635757	0.00051556	0.02072359	0.0008206	0.027941947	1	0.0007895	0.03543767

ILMN_2450491	TRFR2	-1.122926835	0.0002995	0.01489206	0.0002995	0.01335371	0.00000472	0.0007333	0.0000173	0.002159478	1	5.74504E-05	0.00761864
ILMN_2790512	1110039B18RIK	-1.123368404	0.0002995	0.01489206	0.0002995	0.01335371	0.00000228	0.0004265	0.0000102	0.001443157	1	9.21504E-05	0.00995203
ILMN_2894450	SNX15	-1.123418502	0.0002995	0.01489206	0.0002995	0.01335371	8.55E-08	0.0000344	6.06E-07	0.000186894	1	1.89821E-05	0.00409055
ILMN_1223966	LOC385959	-1.123693602	0.00122569	0.03054155	0.00149689	0.03284241	0.00280154	0.05916668	0.00128214	0.036191446	0	0.001686537	0.05325863
ILMN_2736347	PRMT7	-1.123726664	0.0002995	0.01489206	0.0002995	0.01335371	1.05E-09	0.00000111	1.93E-09	0.00000357	1	2.60834E-07	0.00041187
ILMN_2491099	XPOT	-1.123742439	0.0002995	0.01489206	0.0002995	0.01335371	0.00000196	0.00037186	0.00000128	0.000311058	1	3.43889E-06	0.00156931
ILMN_1232396	EAR2	-1.123772011	0.06497475	0.31131649	0.06269472	0.3035407	0.05031812	0.28834804	0.06049753	0.307739355	0	0.057275046	0.32303182
ILMN_1218602	G6PC3	-1.124251076	0.00276802	0.05133777	0.00176049	0.03635757	0.00027886	0.01369203	0.00034532	0.015942739	0	0.001531347	0.05016159
ILMN_3135781	ANXA3	-1.124627391	0.00122569	0.03054155	0.0006399	0.01941092	0.0000259	0.00247667	0.0000866	0.006296133	1	0.000873828	0.03714525
ILMN_2892376	DHX29	-1.124906344	0.0002995	0.01489206	0.0002995	0.01335371	9.49E-07	0.00021238	0.00000258	0.000529628	1	2.384E-06	0.00130551
ILMN_3161878	BID	-1.124973739	0.0002995	0.01489206	0.0002995	0.01335371	0.00000056	0.00014321	5.74E-07	0.000179299	1	2.61375E-06	0.00136712
ILMN_2847787	EMR1	-1.125484607	0.00420612	0.06669083	0.00276802	0.04845153	0.0000979	0.00654917	0.0007017	0.025381142	0	0.00388914	0.08408165
ILMN_2646878	BLMH	-1.12551314	0.0002995	0.01489206	0.0002995	0.01335371	0.00000334	0.00057008	0.0000062	0.001053987	1	1.41013E-05	0.00347315
ILMN_2706853	SCAMP1	-1.125532389	0.0002995	0.01489206	0.0002995	0.01335371	4.75E-07	0.00012706	8.24E-07	0.00022965	1	1.41024E-05	0.00347315
ILMN_2843698	SMARCAL1	-1.125762101	0.0002995	0.01489206	0.0002995	0.01335371	0.00000964	0.00121216	0.0000268	0.002862094	1	2.65234E-05	0.00480383
ILMN_2717366	OASL1	-1.125975138	0.0006399	0.0211535	0.0002995	0.01335371	0.00013051	0.00798826	0.0000663	0.005180373	1	0.000317538	0.02078825
ILMN_2546073	WDR68	-1.126231678	0.0002995	0.01489206	0.0002995	0.01335371	1.61E-07	0.0000542	2.79E-07	0.000110081	1	2.86522E-06	0.00144964
ILMN_3128907	CD63	-1.126420996	0.00176049	0.0385938	0.00149689	0.03284241	0.00054271	0.02136604	0.00067862	0.02485273	1	0.002387591	0.06387081
ILMN_2678355	AMIGO2	-1.126430355	0.0002995	0.01489206	0.0002995	0.01335371	9.13E-08	0.000036	1.85E-07	0.0000834	1	2.65193E-05	0.00480383
ILMN_2655895	AKT2	-1.126825454	0.0002995	0.01489206	0.0002995	0.01335371	2.01E-07	0.0000653	1.53E-07	0.0000735	1	1.49656E-06	0.00102442
ILMN_2625114	CDKAL1	-1.127010951	0.00122569	0.03054155	0.00094262	0.02430167	0.00000936	0.00118696	0.0000213	0.002477176	1	5.52021E-05	0.00760204
ILMN_2667384	SLC6A9	-1.127361604	0.0002995	0.01489206	0.0002995	0.01335371	0.00000932	0.00118696	0.0000174	0.002159478	1	0.000246108	0.01770572
ILMN_1222988	LOC386268	-1.127498485	0.00094262	0.02607154	0.0002995	0.01335371	0.00058613	0.02242668	0.00019971	0.011313575	1	0.001104095	0.04229821
ILMN_2895557	GFI1B	-1.127535545	0.0006399	0.0211535	0.0002995	0.01335371	0.00000674	0.00095405	0.0000135	0.001778728	1	7.88278E-05	0.00901523
ILMN_2925653	EAR2	-1.127584391	0.04792887	0.26510337	0.0460496	0.2570874	0.02741967	0.21097335	0.04301028	0.260513034	0	0.073688628	0.36208008
ILMN_1216972	CLEC4E	-1.128106489	0.00373333	0.06184411	0.0020184	0.03953445	0.00014878	0.00879971	0.0003322	0.01550964	0	0.007560831	0.11797989
ILMN_2652385	BAZ2A	-1.128274842	0.0020184	0.04200694	0.0020184	0.03953445	0.00086242	0.02851067	0.00124947	0.035680505	1	0.001482614	0.04961268
ILMN_3158659	C230096C10RIK	-1.128382209	0.00149689	0.03478153	0.00094262	0.02430167	0.00022091	0.01167139	0.00013978	0.008999194	1	0.000966442	0.03935694
ILMN_2675223	CD33	-1.128563646	0.00094262	0.02607154	0.0006399	0.01941092	0.00001	0.00123611	0.0000453	0.004030508	1	0.000844832	0.03651291
ILMN_2609073	MGAT4B	-1.128660345	0.0002995	0.01489206	0.0002995	0.01335371	0.0000179	0.00186806	0.00013637	0.008839388	1	0.000204627	0.01592867
ILMN_2588055	ACTB	-1.128864948	0.31306407	0.64308013	0.32394852	0.65411508	0.24448523	0.59865801	0.32099244	0.661760783	0	0.345393797	0.69414296
ILMN_2680686	ALG12	-1.129043435	0.0002995	0.01489206	0.0002995	0.01335371	0.0000444	0.00364378	0.0000134	0.001768921	1	1.29447E-05	0.00332893
ILMN_1219820	1200002N14RIK	-1.129152823	0.0006399	0.0211535	0.0006399	0.01941092	0.00000983	0.00121884	0.0000795	0.0059192	1	9.95836E-05	0.01046347
ILMN_2589893	TBRG4	-1.129261707	0.0006399	0.0211535	0.0006399	0.01941092	0.00017752	0.00983669	0.00024679	0.012817366	1	0.00036664	0.02284602
ILMN_2975312	FCER2A	-1.129737894	0.00252097	0.04839275	0.0020184	0.03953445	0.00029365	0.01413478	0.00040153	0.017418469	1	0.002243019	0.06192516
ILMN_2667033	ZXDC	-1.130679589	0.0002995	0.01489206	0.0002995	0.01335371	0.00000237	0.0004394	0.0000082	0.00127918	1	2.34111E-05	0.00450296
ILMN_2622671	ACSL1	-1.131479516	0.0006399	0.0211535	0.0002995	0.01335371	3.66E-07	0.00010462	8.01E-07	0.000227328	1	9.15833E-06	0.00268109
ILMN_2674324	THOP1	-1.131537424	0.0006399	0.0211535	0.0006399	0.01941092	0.0000524	0.00405887	0.00013374	0.008742949	1	0.000486846	0.02669165
ILMN_1259290	AKT3	-1.131538979	0.0002995	0.01489206	0.0002995	0.01335371	6.4E-08	0.0000271	2.38E-07	0.000101599	1	3.28593E-06	0.00154495
ILMN_2932539	RING1	-1.132133147	0.0002995	0.01489206	0.0002995	0.01335371	6.86E-07	0.00016462	7.68E-07	0.000219738	1	2.15328E-05	0.0043202
ILMN_1253819	PRKAR2B	-1.132148923	0.0002995	0.01489206	0.0002995	0.01335371	2.15E-08	0.0000125	1.03E-07	0.0000554	1	5.39498E-06	0.00202516
ILMN_2995688	EG433016	-1.132494728	0.01944482	0.1617544	0.01642977	0.14555842	0.00686131	0.09782114	0.01011034	0.119739224	0	0.023367993	0.21022612
ILMN_1238640	2310003H01RIK	-1.132552815	0.0006399	0.0211535	0.0006399	0.01941092	0.0000179	0.00186806	0.0000445	0.003979315	1	0.000264806	0.01861919
ILMN_2696696	GYPA	-1.132817135	0.00276802	0.05133777	0.00149689	0.03284241	0.0000495	0.00391795	0.00035484	0.016129651	0	0.00270263	0.06885567
ILMN_1225192	NFKBID	-1.133066098	0.0002995	0.01489206	0.0002995	0.01335371	3.36E-10	5.04E-07	1.02E-09	0.00000206	1	6.54696E-08	0.00025395
ILMN_1243066	IL1A	-1.133413071	0.02008879	0.16526703	0.01426212	0.13387405	0.00667676	0.09657646	0.00714689	0.098567729	0	0.046032778	0.29096791
ILMN_2937320	SCHIP1	-1.133751669	0.00094262	0.02607154	0.0002995	0.01335371	0.0000122	0.00143971	0.0000348	0.003370933	1	0.000176289	0.01444673

ILMN_2731237	D8ERTD82E	-1.134047583	0.0002995	0.01489206	0.0002995	0.01335371	0.0000214	0.00216179	0.0000762	0.005756583	1	0.00040803	0.02413289
ILMN_2599657	FMNL3	-1.134171185	0.0002995	0.01489206	0.0002995	0.01335371	0.00000477	0.00073484	0.00000943	0.00136995	1	1.81963E-05	0.00399552
ILMN_2731550	BRP17	-1.134397653	0.0002995	0.01489206	0.0002995	0.01335371	0.00000353	0.00059317	0.00000482	0.000858959	1	6.47271E-05	0.00803428
ILMN_2762189	GPATCH1	-1.134466014	0.0002995	0.01489206	0.0002995	0.01335371	3.36E-08	0.0000172	7.56E-07	0.000219513	1	9.99092E-06	0.00281847
ILMN_2959291	UPP1	-1.13449718	0.00094262	0.02607154	0.00094262	0.02430167	0.00041631	0.01805945	0.00028061	0.013898949	1	0.001301631	0.04617913
ILMN_2841289	TNFAIP2	-1.134827216	0.0002995	0.01489206	0.0002995	0.01335371	0.00000721	0.00099242	0.00000322	0.00064069	1	3.26018E-05	0.00557911
ILMN_2671411	KLC1	-1.135147123	0.0002995	0.01489206	0.0002995	0.01335371	5.07E-08	0.0000227	3.61E-07	0.00013352	1	5.15939E-06	0.0020181
ILMN_2596522	MT1	-1.135343672	0.0002995	0.01489206	0.0002995	0.01335371	0.00000371	0.00061709	4.42E-07	0.000148085	1	1.41024E-05	0.00347315
ILMN_2939681	LYZS	-1.136569055	0.0056004	0.08017457	0.00444101	0.06659434	0.00127184	0.03607589	0.0015594	0.040474884	0	0.004644853	0.0931111
ILMN_2964076	TSPAN31	-1.137017412	0.00122569	0.03054155	0.00094262	0.02430167	0.00012131	0.00760514	0.00019258	0.011039321	1	0.000504223	0.02732257
ILMN_2692797	SLC11A1	-1.137029044	0.00094262	0.02607154	0.0002995	0.01335371	0.0000212	0.00215125	0.0000583	0.004702444	1	0.001259689	0.04555924
ILMN_2693124	RAB1B	-1.137428102	0.01965954	0.16292455	0.01142074	0.11750706	0.00353484	0.06674889	0.00513165	0.08285783	0	0.015623977	0.17119804
ILMN_1220769	LMAN2L	-1.138159096	0.0002995	0.01489206	0.0002995	0.01335371	1.01E-08	0.00000691	8.75E-08	0.0000485	1	5.74828E-07	0.00056929
ILMN_2701271	PLSCR1	-1.138607055	0.0002995	0.01489206	0.0002995	0.01335371	1.15E-07	0.0000431	5.41E-08	0.0000344	1	5.21457E-07	0.00053938
ILMN_2778289	CXCL2	-1.140544603	0.0264868	0.19288541	0.01404445	0.132649	0.0022071	0.05134118	0.00600321	0.089676275	0	0.041147128	0.27693959
ILMN_1249362	LOC386298	-1.141212883	0.00122569	0.03054155	0.00122569	0.02881591	0.00022562	0.01181303	0.00059102	0.022623651	1	0.001141234	0.04287409
ILMN_2661287	AKP2	-1.141256855	0.0002995	0.01489206	0.0002995	0.01335371	4.01E-07	0.00011255	7.15E-07	0.000216027	1	3.59833E-06	0.00158025
ILMN_2846865	ACTB	-1.141333782	0.27330516	0.60657516	0.28441349	0.61784421	0.20397044	0.5535661	0.27555162	0.619558566	0	0.257914169	0.61888498
ILMN_2925711	DUSP6	-1.142932506	0.0006399	0.0211535	0.0002995	0.01335371	9.85E-07	0.00021734	0.0000039	0.000746457	1	4.70154E-05	0.00688184
ILMN_2803674	S100A9	-1.1442518	0.0020184	0.04200694	0.00094262	0.02430167	0.00032351	0.01511104	0.00019143	0.01098713	1	0.001633268	0.05224999
ILMN_2866276	CSF2RA	-1.144341375	0.0002995	0.01489206	0.0002995	0.01335371	0.0000165	0.00178433	0.0000775	0.005835203	1	0.00040803	0.02413289
ILMN_2524986	EAR3	-1.144901605	0.01707784	0.15127561	0.01858605	0.1562833	0.01561583	0.15736519	0.02212242	0.183826235	0	0.019643695	0.19233384
ILMN_2479717	PILRA	-1.145002307	0.0002995	0.01489206	0.0002995	0.01335371	0.00000201	0.000379	0.00000853	0.001297207	1	2.65234E-05	0.00480383
ILMN_2987709	SLC15A3	-1.145009054	0.0002995	0.01489206	0.0002995	0.01335371	0.0000166	0.00178433	0.0000144	0.001881854	1	0.000212368	0.01604723
ILMN_1224736	ZMIZ1	-1.145106147	0.0002995	0.01489206	0.0002995	0.01335371	0.0000174	0.00183609	0.0000098	0.001399019	1	2.34111E-05	0.00450296
ILMN_3155815	9830134C10RIK	-1.145114089	0.0002995	0.01489206	0.0002995	0.01335371	2.35E-07	0.0000718	0.00000169	0.000383182	1	6.16514E-06	0.0021257
ILMN_2654754	GP38	-1.146427658	0.00854165	0.10305721	0.0056004	0.0767776	0.00506605	0.08253748	0.00357137	0.067411346	0	0.016875145	0.17884503
ILMN_3104139	RBM12	-1.147016272	0.0002995	0.01489206	0.0002995	0.01335371	1.43E-08	0.00000901	1.38E-08	0.0000126	1	1.15863E-07	0.00029962
ILMN_2712986	CHI3L3	-1.147371605	0.00122569	0.03054155	0.00149689	0.03284241	0.00087512	0.02868922	0.00073982	0.026207168	1	0.004127635	0.08709385
ILMN_2757368	CRELD2	-1.147374056	0.0002995	0.01489206	0.0002995	0.01335371	2.3E-09	0.00000185	1.18E-08	0.0000119	1	2.74304E-07	0.00041187
ILMN_2491202	VNN3	-1.148153174	0.0002995	0.01489206	0.0002995	0.01335371	4.51E-09	0.00000339	8.56E-09	0.0000105	1	2.24455E-07	0.00037313
ILMN_1230766	SCMH1	-1.148605754	0.0002995	0.01489206	0.0002995	0.01335371	4.83E-08	0.0000223	1.86E-07	0.0000834	1	4.93323E-06	0.00196262
ILMN_2771380	CD52	-1.149676808	0.00898742	0.10547593	0.0076447	0.09407685	0.00210007	0.0498312	0.00636866	0.092696085	0	0.009693098	0.13460577
ILMN_1230708	CLEC4A1	-1.149760601	0.0002995	0.01489206	0.0002995	0.01335371	1.72E-07	0.0000571	0.00000112	0.000290018	1	1.53585E-05	0.00359242
ILMN_2684575	PCYOX1L	-1.149890332	0.00122569	0.03054155	0.0006399	0.01941092	0.0000565	0.00431632	0.00014233	0.009037925	1	0.000438006	0.02507734
ILMN_1218347	MYLK	-1.151233811	0.0002995	0.01489206	0.0002995	0.01335371	1.44E-09	0.00000136	5.7E-09	0.00000758	1	3.34766E-07	0.00044521
ILMN_2601946	5033414K04RIK	-1.151524006	0.0002995	0.01489206	0.0002995	0.01335371	0.00000259	0.00046493	0.00000166	0.000379819	1	0.000317538	0.02078825
ILMN_2835117	CCL7	-1.1516614	0.0002995	0.01489206	0.0002995	0.01335371	7.99E-07	0.00018585	0.00000889	0.001330104	1	9.5799E-05	0.01018072
ILMN_2759484	C3	-1.152531108	0.0006399	0.0211535	0.0002995	0.01335371	0.0000685	0.00500185	0.0000487	0.004231895	1	0.000438006	0.02507734
ILMN_1223416	FER1L3	-1.152772279	0.0002995	0.01489206	0.0002995	0.01335371	4.78E-08	0.0000223	3.94E-07	0.00013797	1	3.99889E-05	0.00618393
ILMN_2901626	TNFRSF21	-1.153121675	0.00094262	0.02607154	0.0006399	0.01941092	0.00000168	0.00033087	0.0000142	0.001859837	1	0.00010758	0.01083883
ILMN_2693895	ACTA2	-1.153348714	0.0002995	0.01489206	0.0002995	0.01335371	0.00000119	0.00025415	0.00000516	0.00090936	1	0.000151664	0.01324485
ILMN_2777498	IL1B	-1.153646647	0.0056004	0.08017457	0.00420612	0.06441203	0.00135477	0.03741307	0.0017555	0.043416704	0	0.004379328	0.09051712
ILMN_2789900	CD177	-1.154670942	0.0006399	0.0211535	0.0002995	0.01335371	0.00000234	0.00043645	0.00000186	0.000412865	1	1.89821E-05	0.00409055
ILMN_2618423	ZXDC	-1.15475865	0.0002995	0.01489206	0.0002995	0.01335371	9.02E-10	9.76E-07	2E-09	0.00000357	1	1.04496E-07	0.00029962
ILMN_1242457	FPR2	-1.155423301	0.00301234	0.05440113	0.0020184	0.03953445	0.00012201	0.00760514	0.00017744	0.010475755	0	0.00093456	0.03863507
ILMN_2742075	CD14	-1.15645531	0.0032539	0.05678214	0.00252097	0.04602629	0.00038681	0.01712826	0.00049905	0.020287507	0	0.001389407	0.04772897

ILMN_2868220	INHBA	-1.156681552	0.00122569	0.03054155	0.00094262	0.02430167	0.00016524	0.00937956	0.00024079	0.012650343	1	0.000470028	0.02607676
ILMN_2674884	SLC11A1	-1.157414839	0.00094262	0.02607154	0.00094262	0.02430167	0.0000257	0.00247314	0.0000641	0.00508011	1	0.000438006	0.02507734
ILMN_3161601	SNCA	-1.157946415	0.0020184	0.04200694	0.00149689	0.03284241	0.00000758	0.00103523	0.0000792	0.005917903	1	0.007351981	0.11667667
ILMN_2705860	TPSAB1	-1.160383394	0.00094262	0.02607154	0.0006399	0.01941092	0.000013	0.00149316	0.00006	0.004813511	1	0.000934606	0.03863507
ILMN_2710905	S100A8	-1.163713512	0.0006399	0.0211535	0.0002995	0.01335371	0.0000119	0.00142619	0.0000147	0.001907372	1	0.000182986	0.01471244
ILMN_2595732	LOC100046232	-1.165021501	0.0002995	0.01489206	0.0002995	0.01335371	0.000001	0.00021909	2.17E-07	0.0000944	1	5.15939E-06	0.0020181
ILMN_2719732	MS4A3	-1.166305486	0.0006399	0.0211535	0.0002995	0.01335371	0.00000901	0.00116445	0.0000212	0.002477176	1	0.000540727	0.02850419
ILMN_1221700	ELA2	-1.167300103	0.0002995	0.01489206	0.0002995	0.01335371	3.27E-09	0.00000253	1.67E-09	0.00000324	1	2.02641E-08	0.00018865
ILMN_1224472	CCL4	-1.167531549	0.00094262	0.02607154	0.0006399	0.01941092	0.00000658	0.0009452	0.0000352	0.003396141	1	0.000255296	0.01817016
ILMN_2728038	ARHGAP24	-1.167825732	0.0002995	0.01489206	0.0002995	0.01335371	4.47E-11	8.33E-08	1.1E-10	0.000000395	1	6.03547E-07	0.00057333
ILMN_1252819	PRMT7	-1.167997376	0.0002995	0.01489206	0.0002995	0.01335371	8.95E-10	9.76E-07	7.15E-10	0.00000159	1	4.07147E-08	0.00024945
ILMN_2538531	LOC386360	-1.168408104	0.0002995	0.01489206	0.0002995	0.01335371	0.00012104	0.00760514	0.00051103	0.020559076	1	0.001104095	0.04229821
ILMN_2493826	UGT1A10	-1.169469481	0.0002995	0.01489206	0.0002995	0.01335371	1.33E-08	0.0000087	8.14E-08	0.0000468	1	3.13951E-06	0.00152224
ILMN_2834379	TGFBI	-1.172758284	0.00176049	0.0385938	0.00122569	0.02881591	0.00093773	0.03009876	0.00024903	0.012894089	1	0.001068077	0.04167292
ILMN_1222543	UGT1A10	-1.173528971	0.0002995	0.01489206	0.0002995	0.01335371	1.46E-09	0.00000136	4.37E-08	0.0000295	1	3.59866E-06	0.00158025
ILMN_2983516	SLC11A1	-1.17650384	0.00122569	0.03054155	0.0006399	0.01941092	0.0000123	0.00144253	0.0000539	0.004524583	1	0.000643034	0.03157309
ILMN_2426480	3830612M24	-1.17764975	0.0006399	0.0211535	0.0002995	0.01335371	7.32E-08	0.0000304	0.00000104	0.000275608	1	9.21504E-05	0.00995203
ILMN_2592554	REXO1	-1.182418789	0.0002995	0.01489206	0.0002995	0.01335371	2.19E-09	0.00000179	2.9E-08	0.0000218	1	7.3257E-07	0.00068198
ILMN_1220548	LRRC41	-1.183163213	0.0002995	0.01489206	0.0002995	0.01335371	2.09E-08	0.0000125	3.74E-07	0.000136	1	9.99092E-06	0.00281847
ILMN_1233336	LOC386199	-1.183990269	0.0006399	0.0211535	0.0006399	0.01941092	0.0000163	0.00177372	0.0000255	0.00279613	1	0.00040803	0.02413289
ILMN_2646985	ATF5	-1.18420231	0.0002995	0.01489206	0.0002995	0.01335371	1.22E-07	0.0000454	0.00000123	0.000301817	1	2.15311E-05	0.0043202
ILMN_2925094	MPO	-1.185131735	0.0002995	0.01489206	0.0002995	0.01335371	0.00000078	0.0001843	0.00000115	0.000292494	1	1.89821E-05	0.00409055
ILMN_1252076	LYZ2	-1.187850205	0.00349473	0.05908105	0.00149689	0.03284241	0.0000728	0.00528008	0.00032836	0.015438431	0	0.002314272	0.06295874
ILMN_2948143	SLC7A11	-1.188505133	0.0002995	0.01489206	0.0002995	0.01335371	5.44E-07	0.00014066	0.00000159	0.000369569	1	0.000120719	0.01149104
ILMN_1219230	LOC100043402	-1.188859089	0.0002995	0.01489206	0.0002995	0.01335371	0.00000132	0.00027167	0.00000103	0.000274668	1	2.15328E-05	0.0043202
ILMN_1230140	LOC385923	-1.189899209	0.0002995	0.01489206	0.0002995	0.01335371	0.00000304	0.00052754	0.0000057	0.000979318	1	3.53859E-05	0.0058616
ILMN_3162125	GRM6	-1.194679101	0.0002995	0.01489206	0.0002995	0.01335371	2.08E-07	0.0000667	1.2E-08	0.0000119	1	4.9657E-07	0.00052531
ILMN_2771176	CCL7	-1.196175382	0.0002995	0.01489206	0.0002995	0.01335371	1.02E-11	2.5E-08	4.19E-10	0.000000976	1	4.07997E-07	0.00049976
ILMN_2847115	GPR109A	-1.199553298	0.0006399	0.0211535	0.0006399	0.01941092	0.00000482	0.0007403	0.0000154	0.001964139	1	0.00011618	0.0112429
ILMN_2758029	PRTN3	-1.205025411	0.0002995	0.01489206	0.0002995	0.01335371	1.53E-10	2.64E-07	3.43E-10	0.00000084	1	5.59305E-08	0.00024945
ILMN_2722996	SIRPA	-1.209776171	0.0002995	0.01489206	0.0002995	0.01335371	1.66E-09	0.00000149	3.18E-09	0.00000462	1	3.28593E-06	0.00154495
ILMN_2657828	RHBDF1	-1.216435604	0.0002995	0.01489206	0.0002995	0.01335371	2.44E-12	9.46E-09	1.36E-10	0.000000429	1	5.89499E-08	0.00024945
ILMN_2712075	LCN2	-1.216711224	0.0006399	0.0211535	0.0002995	0.01335371	0.00000262	0.00046695	0.00000288	0.000577427	1	2.44059E-05	0.00463717
ILMN_2878071	LYZ	-1.22864681	0.0002995	0.01489206	0.0002995	0.01335371	5.41E-08	0.000024	0.00000139	0.000336099	1	7.57938E-05	0.00879794
ILMN_2705628	CLEC4D	-1.228745779	0.0006399	0.0211535	0.0006399	0.01941092	0.00000062	0.00015362	0.0000039	0.000746457	1	7.0054E-05	0.00846962
ILMN_1233982	LOC270589	-1.22932799	0.0002995	0.01489206	0.0002995	0.01335371	0.00000694	0.00097871	0.00000394	0.000746457	1	4.51564E-05	0.00675851
ILMN_1377923	ACTB	-1.230879389	0.07635019	0.3372365	0.05022289	0.26966529	0.00918324	0.11590351	0.03014873	0.215797746	0	0.014835081	0.16656218
ILMN_1249030	MPO	-1.231747939	0.0002995	0.01489206	0.0002995	0.01335371	0.0000017	0.00033473	0.0000195	0.002344998	1	0.00022037	0.01646479
ILMN_2538242	LOC386144	-1.239189285	0.0002995	0.01489206	0.0002995	0.01335371	0.000015	0.00166908	0.0000107	0.001483462	1	0.000135361	0.01242731
ILMN_2993314	CLEC4N	-1.244916169	0.0006399	0.0211535	0.0002995	0.01335371	0.00000115	0.00024883	0.000015	0.001929689	1	0.000163541	0.01374071
ILMN_2750842	2610027L16RIK	-1.245539485	0.0002995	0.01489206	0.0002995	0.01335371	0.00000254	0.00046434	0.00000545	0.000950899	1	6.44447E-06	0.00218957
ILMN_2600421	MPO	-1.29293209	0.0002995	0.01489206	0.0002995	0.01335371	8.09E-10	9.34E-07	2.37E-08	0.0000187	1	8.76731E-06	0.00261597
ILMN_2763245	CXCL1	-1.3	0.0006399	0.0211535	0.0002995	0.01335371	2.37E-07	0.0000718	0.00000181	0.000406	1	9.95836E-05	0.01046347
ILMN_1253874	SERPINB2	-1.31	0.0002995	0.01489206	0.0002995	0.01335371	6.55E-10	8.24E-07	9.01E-09	0.0000105	1	2.38377E-06	0.00130551
ILMN_1215076	F830002E14RIK	-1.32	0.0020184	0.04200694	0.00122569	0.02881591	0.00115136	0.03420847	0.000886	0.0292	1	0.001344859	0.0469611
ILMN_2725259	IL2	-1.37	0.0002995	0.01489206	0.0002995	0.01335371	5.55E-14	6.46E-10	1.82E-11	0.000000121	1	9.40233E-09	0.00012222

Supplementary Table 2:

Mouse splenocyte study: Outputs of cell-type enrichment analyses showing enrichment for cell types including regulatory T cells (Tregs) among genes upregulated by Copaxone, and enrichment for cell types including monocytes among genes upregulated by Natco (Towfic et al, Table S8).

TABLE S8									
	4-method_up GA					4-method_up generic			
Sample ID	Score	p-value	adjusted p-value		Sample ID	Score	p-value	adjusted p-value	
T.8Nve.Sp.OT1.rnk	78.016717	1.30E-93	3.14E-92		MF.Lu.rnk	52.365983	4.74E-19	5.33E-18	
T.4FP3.25..LN.rnk	77.258574	4.58E-92	9.88E-91		MF.BM.rnk	52.167673	8.50E-27	4.12E-25	
CD4Control.rnk	74.792428	5.10E-82	4.95E-81		Mo.6C.II..BM.rnk	51.566882	3.63E-25	1.41E-23	
CD4TESTCJ.rnk	74.304957	7.18E-100	3.48E-98		SC.GMP.BM.rnk	51.558744	7.77E-33	7.53E-31	
T.4Nve.Sp.rnk	74.117612	6.71E-104	6.51E-102		MF.11cloSer.SI.rnk	46.967776	2.67E-16	1.56E-15	
T.8SP24..Th.rnk	73.133104	6.90E-91	1.34E-89		MLP.FL.rnk	46.519979	7.74E-32	5.01E-30	
T.8Nve.LN.rnk	72.608165	2.84E-97	7.86E-96		MF.Thio5.II.480int.PC.rnk	46.093861	1.84E-18	1.55E-17	
T.4SP24..Th.rnk	70.766828	3.66E-98	1.18E-96		MF.Thio5.II.480hi.PC.rnk	45.202935	2.74E-16	1.56E-15	
T.8Nve.MLN.rnk	69.029666	2.66E-98	1.03E-96		MF.103.11b..SI.rnk	45.121929	6.17E-10	1.93E-09	
T.8SP24int.Th.rnk	64.965353	5.23E-76	4.06E-75		MF.II.480hi.PC.rnk	42.259112	5.29E-17	3.66E-16	
T.4Nve.LN.rnk	63.682185	1.43E-100	9.23E-99		MF.11cloSer.Salm3.SI.rnk	40.791601	2.09E-15	1.04E-14	
CD4TESTJS.rnk	60.571137	1.45E-90	2.56E-89		MF.II.480lo.PC.rnk	39.348471	1.11E-20	1.66E-19	
Tgd.vg2..Sp.rnk	59.521782	1.14E-81	1.05E-80		MF.103.11b..Salm3.SI.rnk	37.916306	4.52E-12	1.79E-11	
T.4Mem.Sp.rnk	58.4054	1.28E-74	9.20E-74		MF.Thio5.II.480lo.PC.rnk	37.295189	6.98E-16	3.87E-15	
T.4Mem44h62l.Sp.rnk	57.606055	1.08E-73	6.98E-73		DC.8..Th.rnk	36.10766	1.28E-16	8.46E-16	

4-method_up GA

Cell type	Score	p-value	adjusted p-value
CD8+ T-cell	78.016717	1.30E-93	3.14E-92
CD4+ T-cell (FOXP3+)	77.258574	4.58E-92	9.88E-91
CD4+ T-cell	74.792428	5.10E-82	4.95E-81
CD4+ T-cell	74.304957	7.18E-100	3.48E-98
CD4+ T-cell	74.117612	6.71E-104	6.51E-102
CD8+ T-cell	73.133104	6.90E-91	1.34E-89
CD8+ T-cell	72.608165	2.84E-97	7.86E-96
CD4+ T-cell	70.766828	3.66E-98	1.18E-96
CD8+ T-cell	69.029666	2.66E-98	1.03E-96
CD8+ T-cell	64.965353	5.23E-76	4.06E-75
CD4+ T-cell	63.682185	1.43E-100	9.23E-99
CD4+ T-cell	60.571137	1.45E-90	2.56E-89

4-method_up generic

Cell type	Score	p-value	adjusted p-value
Macrophage Cell	52.365983	4.74E-19	5.33E-18
Macrophage Cell	52.167673	8.50E-27	4.12E-25
MONOCYTE CELL	51.566882	3.63E-25	1.41E-23
Stromal Cell	51.558744	7.77E-33	7.53E-31
Macrophage Cell	46.967776	2.67E-16	1.56E-15
Multi-lineage Progenitor	46.519979	7.74E-32	5.01E-30
Macrophage Cell	46.093861	1.84E-18	1.55E-17
Macrophage Cell	45.202935	2.74E-16	1.56E-15
Macrophage Cell	45.121929	6.17E-10	1.93E-09
Macrophage Cell	42.259112	5.29E-17	3.66E-16
Macrophage Cell	40.791601	2.09E-15	1.04E-14
Macrophage Cell	39.348471	1.11E-20	1.66E-19

Gamma Delta T-Cell	59.521782	1.14E-81	1.05E-80
CD4+ T-cell	58.4054	1.28E-74	9.20E-74
CD4+ T-cell	57.606055	1.08E-73	6.98E-73

Macrophage Cell	37.916306	4.52E-12	1.79E-11
Macrophage Cell	37.295189	6.98E-16	3.87E-15
Dendritic Cell	**36.10766**	**1.28E-16**	**8.46E-16**

	UP_in_GA				DOWN_in_GA			
Sample ID	Score	p-value	adjusted p-value		Sample ID	Score	p-value	adjusted p-value
Tgd.vg2.24ahi.e17.Th.rnk	55.300114	9.65E-11	2.27E-09		MF.Thio5.II.480int.PC.rnk	78.362994	7.87E-13	6.06E-11
Tgd.vg1.vd6.24ahi.Th.rnk	51.659013	1.41E-11	5.31E-10		MF.103.11b..SI.rnk	70.679218	1.05E-05	5.38E-05
T.8Eff.Sp.OT1.d5.VSVOva.rnk	49.385908	3.58E-15	3.37E-13		MF.11cloSer.SI.rnk	70.056104	8.81E-09	6.46E-08
Tgd.vg3.24alo.e17.Th.rnk	48.443386	1.36E-10	2.57E-09		MF.Thio5.II.480hi.PC.rnk	69.920643	4.45E-10	7.61E-09
T.8Eff.Sp.OT1.d6.LisOva.rnk	44.787648	5.19E-11	1.39E-09		MF.11cloSer.Salm3.SI.rnk	66.685274	3.26E-12	1.25E-10
NKT.44.NK1.1..Th.rnk	44.353764	5.06E-07	3.07E-06		MF.103.11b..Salm3.SI.rnk	62.942816	1.69E-09	1.63E-08
T.8SP24int.Th.rnk	42.865925	4.45E-08	4.92E-07		GN.BM.rnk	60.965868	3.15E-10	6.06E-09
T.DPbl.Th.rnk	42.195941	7.68E-10	1.31E-08		MF.Lu.rnk	58.386331	8.60E-11	2.21E-09
Tgd.vg5.24ahi.Th.rnk	40.991976	3.97E-12	1.86E-10		MF.II.480hi.PC.rnk	55.697691	9.43E-10	1.25E-08
T.8Eff.Sp.OT1.48hr.LisOva.rnk	40.833999	8.39E-07	4.78E-06		GN.Thio.PC.rnk	53.404852	8.61E-11	2.21E-09
T.4FP3.25..LN.rnk	40.093191	1.51E-05	5.06E-05		GN.Arth.BM.rnk	53.148698	1.07E-09	1.26E-08
T.4Mem.Sp.rnk	40.034017	6.10E-06	2.39E-05		MF.RP.Sp.rnk	50.282383	1.63E-09	1.63E-08
T.8SP24..Th.rnk	39.397607	1.32E-07	1.25E-06		MF.Thio5.II.480lo.PC.rnk	50.16729	6.62E-09	5.10E-08
T.4SP24..Th.rnk	37.645363	1.91E-09	2.56E-08		Mo.6C.II..LN.rnk	49.39474	9.73E-10	1.25E-08
T.4Mem44h62l.Sp.rnk	36.123266	2.52E-06	1.21E-05		Mo.6C.II..BM.rnk	49.223068	1.60E-08	1.07E-07

UP_in_GA

	Score	**p-value**	**adjusted p-value**
Gamma Delta T-Cell	55.300114	9.648E-11	2.267E-09
Gamma Delta T-Cell	51.659013	1.412E-11	5.308E-10
CD8+ T-cell	49.385908	3.581E-15	3.366E-13
Gamma Delta T-Cell	48.443386	1.365E-10	2.565E-09
CD8+ T-cell	44.787648	5.188E-11	1.393E-09
Natural Killer T-Cell	44.353764	5.056E-07	3.066E-06
CD8+ T-cell	42.865925	4.449E-08	4.921E-07
CD4+ CD8+ T-cell blast	42.195941	7.676E-10	1.312E-08

DOWN_in_GA

	Score	**p-value**	**adjusted p-value**
Macrophage	78.362994	7.873E-13	6.063E-11
Macrophage	70.679218	1.048E-05	5.38E-05
Macrophage	70.056104	8.813E-09	6.463E-08
Macrophage	69.920643	4.449E-10	7.613E-09
Macrophage	66.685274	3.257E-12	1.254E-10
Macrophage	62.942816	1.689E-09	1.625E-08
Granulocytes	**60.965868**	**3.145E-10**	**6.055E-09**
Macrophage	58.386331	8.602E-11	2.209E-09

Gamma Delta T-Cell	40.991976	3.967E-12	1.864E-10
CD8+ T-cell	40.833999	8.385E-07	4.777E-06
CD4+ T-cell (FOXP3+)	40.093191	1.507E-05	5.06E-05
CD4+ T-cell	40.034017	6.104E-06	2.391E-05
CD8+ T-cell	39.397607	1.325E-07	1.245E-06
CD4+ T-cell	37.645363	1.91E-09	2.565E-08
CD4+ T-cell	36.123266	2.516E-06	1.213E-05

Macrophage	55.697691	9.426E-10	1.249E-08
Granulocytes	53.404852	8.606E-11	2.209E-09
Granulocytes	53.148698	1.067E-09	1.264E-08
Macrophage	50.282383	1.628E-09	1.625E-08
Macrophage	50.16729	6.621E-09	5.098E-08
MONOCYTE CELL	49.39474	9.734E-10	1.249E-08
MONOCYTE CELL	49.223068	1.601E-08	1.072E-07

	UP_in_generic				DOWN_in_generic			
Sample ID	Score	p-value	adjusted p-value	Sample ID	Score	p-value	adjusted p-value	
FRC.MLN.rnk	52.352931	3.50E-12	1.89E-10	CD4Control.rnk	27.128445	2.16E-11	8.40E-10	
FRC.SLN.rnk	50.863086	4.71E-10	9.54E-09	T.4SP24..Th.rnk	25.703994	2.33E-10	3.70E-09	
Fi.Sk.rnk	50.416456	5.96E-11	1.61E-09	CD4TESTCJ.rnk	25.048321	4.40E-11	1.22E-09	
LEC.SLN.rnk	50.342848	8.82E-07	6.81E-06	T.8Nve.Sp.OT1.rnk	23.837814	6.69E-10	7.63E-09	
MF.Thio5.II.480hi.PC.rnk	46.614424	2.72E-12	1.89E-10	T.4FP3.25..LN.rnk	23.830619	3.47E-09	2.59E-08	
LEC.MLN.rnk	43.323945	4.18E-07	3.57E-06	T.4Nve.Sp.rnk	23.597706	3.09E-10	4.28E-09	
St.31.38.44..SLN.rnk	41.849758	1.77E-08	2.60E-07	T.4SP69..Th.rnk	22.613314	4.58E-13	2.22E-11	
BEC.SLN.rnk	39.075496	5.58E-06	3.62E-05	T.8SP24int.Th.rnk	22.204889	2.66E-08	1.47E-07	
BEC.MLN.rnk	38.258788	1.37E-05	8.55E-05	T.8SP24..Th.rnk	21.831712	1.02E-08	6.17E-08	
MF.Thio5.II.480int.PC.rnk	38.151955	1.13E-11	4.56E-10	T.4SP24int.Th.rnk	21.588615	7.01E-14	6.80E-12	
Fi.MTS15..Th.rnk	34.64529	4.61E-05	2.34E-04	T.8Eff.Sp.OT1.d6.LisOva.rn	20.621541	9.85E-07	3.61E-06	
MF.BM.rnk	32.936497	6.48E-08	7.50E-07	Tgd.vg2.24ahi.e17.Th.rnk	20.390136	6.79E-04	0.0016877	
MF.103.11b..SI.rnk	32.877997	1.54E-05	9.22E-05	T.4Mem44h62l.LN.rnk	20.158235	4.92E-09	3.41E-08	
MF.II.480lo.PC.rnk	31.911268	9.99E-09	1.62E-07	T.8Nve.LN.rnk	19.500055	8.43E-10	9.09E-09	
MF.II.480hi.PC.rnk	31.785718	6.25E-07	5.06E-06	T.4Mem.Sp.rnk	19.281602	1.35E-09	1.25E-08	

UP_in_generic

	Score	**p-value**	**adjusted p-value**
fibroblastic reticular cell	**52.352931**	**3.497E-12**	**1.889E-10**
fibroblastic reticular cell	**50.863086**	**4.711E-10**	**9.539E-09**
fibroblast	**50.416456**	**5.964E-11**	**1.61E-09**

DOWN_in_generic

	Score	**p-value**	**adjusted p-value**
CD4+ T-cell	27.128445	2.16E-11	8.40E-10
CD4+ T-cell	25.703994	2.33E-10	3.70E-09
CD4+ T-cell	25.048321	4.40E-11	1.22E-09

lymphatic endothelial cell	50.342848	8.823E-07	6.806E-06
Macrophages	46.614424	2.72E-12	1.89E-10
lymphatic endothelial cell	43.323945	4.183E-07	3.567E-06
Stromal Cell	41.849758	1.772E-08	2.603E-07
blood endothelial cell	39.075496	5.581E-06	3.616E-05
blood endothelial cell	38.258788	1.372E-05	8.55E-05
Macrophages	38.151955	1.13E-11	4.56E-10
fibroblast	34.64529	4.613E-05	0.0002335
Macrophages	32.936497	6.48E-08	7.50E-07
Macrophages	32.877997	1.54E-05	9.22E-05
Macrophages	31.911268	9.99E-09	1.62E-07
Macrophages	31.785718	6.25E-07	5.06E-06

CD8+ T-cell	23.837814	6.69E-10	7.63E-09
***CD4+ T-cell (FOXP3+)*	23.830619	3.468E-09	2.587E-08
CD4+ T-cell	23.597706	3.09E-10	4.28E-09
CD4+ T-cell	22.613314	4.58E-13	2.22E-11
CD8+ T-cell	22.204889	2.66E-08	1.47E-07
CD8+ T-cell	21.831712	1.02E-08	6.17E-08
CD4+ T-cell	21.588615	7.01E-14	6.80E-12
CD8+ T-cell	20.621541	9.85E-07	3.61E-06
Gamma Delta T-Cell	20.390136	6.79E-04	0.0016877
CD4+ T-cell	20.158235	4.92E-09	3.41E-08
CD8+ T-cell	19.500055	8.43E-10	9.09E-09
CD4+ T-cell	19.281602	1.35E-09	1.25E-08

Supplementary Table 3:

Mouse splenocyte study: Enrichment for genes higher in Copaxone than Natco by the Wilcoxon rank sum test, including FoxP3 targets among the enriched signatures (Towfic et al, Table S6).

TABLE S6							
Reference Set	User Set	N	K	n	k	P	BHP_P
BLALOCK_ALZHEIMERS_DISEASE_UP	wilcox_up_in_GA	31847	1691	392	54	0	0
PILON_KLF1_TARGETS_DN	wilcox_up_in_GA	31847	1972	392	80	0	0
MEMBRANE	wilcox_up_in_GA	31847	1994	392	65	0	0
GRAESSMANN_APOPTOSIS_BY_DOXORUBICIN_DN	wilcox_up_in_GA	31847	1781	392	60	0	0
GGGAGGRR_V$MAZ_Q6	wilcox_up_in_GA	31847	2274	392	69	0	0
SIGNAL_TRANSDUCTION	wilcox_up_in_GA	31847	1634	392	60	0	0
TTGTTT_V$FOXO4_01	wilcox_up_in_GA	31847	2061	392	64	0	0
DUTERTRE_ESTRADIOL_RESPONSE_24HR_DN	wilcox_up_in_GA	31847	505	392	30	0	0
GNF2_MATK	wilcox_up_in_GA	31847	25	392	10	0	0
PID_TCR_PATHWAY	wilcox_up_in_GA	31847	66	392	14	3.55E-12	8.55E-10
MEMBRANE_PART	wilcox_up_in_GA	31847	1670	392	53	8.99E-12	1.97E-09
BIOPOLYMER_METABOLIC_PROCESS	wilcox_up_in_GA	31847	1684	392	53	1.10E-11	2.20E-09
PID_CD8TCRDOWNSTREAMPATHWAY	wilcox_up_in_GA	31847	65	392	12	4.02E-11	7.45E-09
REACTOME_TCR_SIGNALING	wilcox_up_in_GA	31847	54	392	13	4.93E-11	8.47E-09
PID_CD8TCRPATHWAY	wilcox_up_in_GA	31847	53	392	12	7.51E-11	1.21E-08
SMID_BREAST_CANCER_NORMAL_LIKE_UP	wilcox_up_in_GA	31847	476	392	48	9.86E-11	1.44E-08
PUJANA_ATM_PCC_NETWORK	wilcox_up_in_GA	31847	1442	392	52	1.02E-10	1.44E-08
GNF2_PTPN4	wilcox_up_in_GA	31847	51	392	11	1.17E-10	1.57E-08
MODULE_64	wilcox_up_in_GA	31847	518	392	28	1.30E-10	1.59E-08
PID_IL12_STAT4PATHWAY	wilcox_up_in_GA	31847	33	392	9	1.37E-10	1.59E-08
ZHENG_BOUND_BY_FOXP3	wilcox_up_in_GA	31847	491	392	56	1.42E-10	1.59E-08
DIAZ_CHRONIC_MEYLOGENOUS_LEUKEMIA_UP	wilcox_up_in_GA	31847	1382	392	51	1.46E-10	1.59E-08
CHEN_METABOLIC_SYNDROM_NETWORK	wilcox_up_in_GA	31847	1210	392	46	1.72E-10	1.79E-08
MODULE_75	wilcox_up_in_GA	31847	399	392	29	1.86E-10	1.80E-08
MODULE_84	wilcox_up_in_GA	31847	549	392	38	1.87E-10	1.80E-08
MARSON_BOUND_BY_FOXP3_UNSTIMULATED	wilcox_up_in_GA	31847	1229	392	66	2.04E-10	1.80E-08
LINDGREN_BLADDER_CANCER_CLUSTER_2B	wilcox_up_in_GA	31847	392	392	29	2.12E-10	1.80E-08
SANSOM_APC_TARGETS_DN	wilcox_up_in_GA	31847	366	392	25	2.16E-10	1.80E-08
MODULE_46	wilcox_up_in_GA	31847	395	392	29	2.27E-10	1.80E-08
SMID_BREAST_CANCER_LUMINAL_B_DN	wilcox_up_in_GA	31847	564	392	30	2.32E-10	1.80E-08
GCACTTT,MIR-17-5P,MIR-20A,MIR-106A,MIR-106B,MI	wilcox_up_in_GA	31847	595	392	33	2.46E-10	1.80E-08
NUYTTEN_EZH2_TARGETS_UP	wilcox_up_in_GA	31847	1037	392	44	2.46E-10	1.80E-08
KUMAR_TARGETS_OF_MLL_AF9_FUSION	wilcox_up_in_GA	31847	405	392	26	2.47E-10	1.80E-08
MARSON_BOUND_BY_FOXP3_STIMULATED	wilcox_up_in_GA	31847	1022	392	54	2.65E-10	1.83E-08
GOBERT_OLIGODENDROCYTE_DIFFERENTIATION_DN	wilcox_up_in_GA	31847	1080	392	44	2.67E-10	1.83E-08
REACTOME_IMMUNE_SYSTEM	wilcox_up_in_GA	31847	933	392	51	2.82E-10	1.88E-08

MODULE_45	wilcox_up_in_GA	31847	583	392	33	2.99E-10	1.95E-08
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MODULE_6	wilcox_up_in_generic	31847	416	439	23	2.30E-08	1.55E-06
RUTELLA_RESPONSE_TO_HGF_UP	wilcox_up_in_generic	31847	418	439	23	2.51E-08	1.65E-06
MODULE_3	wilcox_up_in_generic	31847	385	439	22	2.59E-08	1.65E-06
CHARAFE_BREAST_CANCER_LUMINAL_VS_BASAL_DN	wilcox_up_in_generic	31847	455	439	24	2.78E-08	1.73E-06
MARTENS_BOUND_BY_PML_RARA_FUSION	wilcox_up_in_generic	31847	456	439	24	2.90E-08	1.75E-06
GNF2_CD33	wilcox_up_in_generic	31847	52	439	9	3.62E-08	2.13E-06
NUCLEOBASENUCLEOSIDENUCLEOTIDE_AND_NUCLEIC	wilcox_up_in_generic	31847	1244	439	43	3.88E-08	2.23E-06
TONKS_TARGETS_OF_RUNX1_RUNX1T1_FUSION_ERYT	wilcox_up_in_generic	31847	157	439	14	4.29E-08	2.41E-06
FOSTER_KDM1A_TARGETS_DN	wilcox_up_in_generic	31847	211	439	16	4.64E-08	2.54E-06
NUYTTEN_EZH2_TARGETS_UP	wilcox_up_in_generic	31847	1037	439	38	5.75E-08	3.05E-06
MARKEY_RB1_ACUTE_LOF_UP	wilcox_up_in_generic	31847	215	439	16	6.02E-08	3.05E-06
CASORELLI_ACUTE_PROMYELOCYTIC_LEUKEMIA_DN	wilcox_up_in_generic	31847	663	439	29	6.04E-08	3.05E-06
MODULE_16	wilcox_up_in_generic	31847	511	439	25	6.11E-08	3.05E-06
BRUINS_UVC_RESPONSE_LATE	wilcox_up_in_generic	31847	1137	439	40	7.46E-08	3.65E-06
ZHANG_TLX_TARGETS_36HR_UP	wilcox_up_in_generic	31847	221	439	16	8.79E-08	4.21E-06
RODWELL_AGING_KIDNEY_UP	wilcox_up_in_generic	31847	487	439	24	9.84E-08	4.61E-06
SEKI_INFLAMMATORY_RESPONSE_LPS_UP	wilcox_up_in_generic	31847	77	439	10	1.08E-07	4.96E-06
HESS_TARGETS_OF_HOXA9_AND_MEIS1_DN	wilcox_up_in_generic	31847	77	439	10	1.08E-07	4.96E-06
IVANOVA_HEMATOPOIESIS_EARLY_PROGENITOR	wilcox_up_in_generic	31847	532	439	25	1.31E-07	5.77E-06
CELLULAR_PROTEIN_METABOLIC_PROCESS	wilcox_up_in_generic	31847	1117	439	39	1.33E-07	5.77E-06
ACEVEDO_LIVER_TUMOR_VS_NORMAL_ADJACENT_TI	wilcox_up_in_generic	31847	863	439	33	1.69E-07	7.21E-06
WANG_IMMORTALIZED_BY_HOXA9_AND_MEIS1_UP	wilcox_up_in_generic	31847	31	439	7	1.78E-07	7.36E-06
RYTTCCTG_V$ETS2_B	wilcox_up_in_generic	31847	1085	439	38	1.80E-07	7.36E-06
CELLULAR_MACROMOLECULE_METABOLIC_PROCESS	wilcox_up_in_generic	31847	1131	439	39	1.83E-07	7.36E-06
KOINUMA_TARGETS_OF_SMAD2_OR_SMAD3	wilcox_up_in_generic	31847	824	439	32	1.86E-07	7.37E-06
KRIGE_RESPONSE_TO_TOSEDOSTAT_24HR_UP	wilcox_up_in_generic	31847	783	439	31	1.91E-07	7.45E-06
MODULE_45	wilcox_up_in_generic	31847	583	439	26	2.03E-07	7.76E-06
RASHI_RESPONSE_TO_IONIZING_RADIATION_2	wilcox_up_in_generic	31847	127	439	12	2.09E-07	7.88E-06
RESPONSE_TO_STRESS	wilcox_up_in_generic	31847	508	439	24	2.13E-07	7.88E-06
LENAOUR_DENDRITIC_CELL_MATURATION_DN	wilcox_up_in_generic	31847	128	439	12	2.28E-07	8.31E-06
MODULE_84	wilcox_up_in_generic	31847	549	439	25	2.37E-07	8.49E-06
GROSS_HYPOXIA_VIA_ELK3_UP	wilcox_up_in_generic	31847	209	439	15	2.48E-07	8.76E-06
GTGCCAA,MIR-96	wilcox_up_in_generic	31847	303	439	18	2.73E-07	9.49E-06
MARTENS_TRETINOIN_RESPONSE_DN	wilcox_up_in_generic	31847	841	439	32	2.92E-07	1.00E-05
MGGAAGTG_V$GABP_B	wilcox_up_in_generic	31847	757	439	30	2.96E-07	1.00E-05
ACEVEDO_LIVER_CANCER_UP	wilcox_up_in_generic	31847	973	439	35	3.01E-07	1.00E-05
NEGATIVE_REGULATION_OF_BIOLOGICAL_PROCESS	wilcox_up_in_generic	31847	677	439	28	3.18E-07	1.04E-05
MODULE_118	wilcox_up_in_generic	31847	410	439	21	3.33E-07	1.08E-05

GAL_LEUKEMIC_STEM_CELL_DN	wilcox_up_in_generic	31847	244	439	16	3.38E-07	1.08E-05
MOOTHA_MITOCHONDRIA	wilcox_up_in_generic	31847	447	439	22	3.44E-07	1.08E-05
LINDSTEDT_DENDRITIC_CELL_MATURATION_A	wilcox_up_in_generic	31847	67	439	9	3.49E-07	1.08E-05
MEMBRANE	wilcox_up_in_generic	31847	1994	439	56	3.55E-07	1.09E-05
TARTE_PLASMA_CELL_VS_PLASMABLAST_DN	wilcox_up_in_generic	31847	309	439	18	3.64E-07	1.10E-05
NEGATIVE_REGULATION_OF_CELLULAR_PROCESS	wilcox_up_in_generic	31847	646	439	27	4.22E-07	1.25E-05
GRAESSMANN_RESPONSE_TO_MC_AND_DOXORUBICI	wilcox_up_in_generic	31847	770	439	30	4.23E-07	1.25E-05
GNF2_CD14	wilcox_up_in_generic	31847	35	439	7	4.35E-07	1.26E-05
RPS14_DN.V1_UP	wilcox_up_in_generic	31847	192	439	14	5.14E-07	1.47E-05
PUJANA_CHEK2_PCC_NETWORK	wilcox_up_in_generic	31847	779	439	30	5.39E-07	1.53E-05
BERENJENO_TRANSFORMED_BY_RHOA_UP	wilcox_up_in_generic	31847	536	439	24	5.57E-07	1.56E-05
CELL_DEVELOPMENT	wilcox_up_in_generic	31847	577	439	25	5.92E-07	1.64E-05
ONDER_CDH1_TARGETS_2_DN	wilcox_up_in_generic	31847	464	439	22	6.44E-07	1.76E-05
REACTOME_ACTIVATED_TLR4_SIGNALLING	wilcox_up_in_generic	31847	93	439	10	6.52E-07	1.76E-05
MTOR_UP.N4.V1_UP	wilcox_up_in_generic	31847	196	439	14	6.59E-07	1.76E-05
CYTOPLASMIC_PART	wilcox_up_in_generic	31847	1383	439	43	6.89E-07	1.82E-05
NEGATIVE_REGULATION_OF_DEVELOPMENTAL_PROC	wilcox_up_in_generic	31847	197	439	14	7.00E-07	1.83E-05
GNF2_HCK	wilcox_up_in_generic	31847	94	439	10	7.21E-07	1.86E-05
COFACTOR_METABOLIC_PROCESS	wilcox_up_in_generic	31847	54	439	8	7.31E-07	1.87E-05
SIGNAL_TRANSDUCTION	wilcox_up_in_generic	31847	1634	439	48	7.57E-07	1.91E-05
PROGRAMMED_CELL_DEATH	wilcox_up_in_generic	31847	432	439	21	7.76E-07	1.94E-05

Supplementary Table 4:

Human monocyte study: probesets significantly modulated by Copaxone relative to mannitol at 6 hours, subject to fold-change and adjusted p value filters of 1.5 and 1e-5, respectively.

Upregulated:

ID	Gene	raw.FC	AveExpr	P.Value	adj.P.Val
201005_at	CD9	3.77232321	10.8126963	1.14E-34	6.23E-30
206835_at	STATH	7.52573433	10.4825707	1.00E-33	2.74E-29
1553982_a_at	RAB7B	2.26468475	11.7452289	1.26E-31	2.30E-27
242871_at	PAQR5	3.9374814	9.90015385	7.51E-31	1.01E-26
1555759_a_at	CCL5	2.21501539	13.5769189	9.21E-31	1.01E-26
228766_at	---	2.3291844	10.5559717	3.35E-30	3.06E-26
209555_s_at	CD36	2.44281389	9.32514677	7.64E-29	5.66E-25
203939_at	NT5E	5.3338766	8.32269063	8.29E-29	5.66E-25
208789_at	PTRF	2.82016222	9.15275301	1.88E-28	1.14E-24
230266_at	RAB7B	2.23824891	11.7520076	2.34E-28	1.28E-24
206488_s_at	CD36	2.15872949	10.8868374	3.67E-28	1.83E-24
208121_s_at	PTPRO	2.14699192	9.81795145	4.30E-28	1.96E-24
203037_s_at	MTSS1	3.1858517	11.4020576	7.89E-28	3.32E-24
1405_i_at	CCL5	2.29122708	13.3028093	2.79E-27	1.06E-23
204655_at	CCL5	2.25036905	13.1626051	2.90E-27	1.06E-23
206171_at	ADORA3	2.10036549	10.0753041	3.42E-27	1.17E-23
219386_s_at	SLAMF8	2.98872777	10.0302719	3.80E-27	1.22E-23
226218_at	---	3.50148157	7.21345525	1.83E-26	5.55E-23
218559_s_at	MAFB	2.64025573	12.4234341	3.40E-26	9.78E-23
223125_s_at	C1ORF21	2.21866076	11.0023707	4.15E-26	1.13E-22
203887_s_at	THBD	1.79337816	12.8191102	4.45E-26	1.15E-22
227265_at	KIAA1505	2.50321069	9.85031558	4.61E-26	1.15E-22
205495_s_at	GNLY	2.40116081	7.73128126	5.34E-26	1.27E-22
216250_s_at	LPXN	2.1444933	11.2374219	1.42E-25	3.23E-22
237252_at	THBD	2.06547107	9.51011605	2.22E-25	4.86E-22
235457_at	MAML2	2.62488399	8.91497905	5.79E-25	1.22E-21
225171_at	ARHGAP18	1.83225951	10.7080346	6.66E-25	1.35E-21
204684_at	NPTX1	2.87807656	10.9346668	1.40E-24	2.74E-21
230925_at	APBB1IP	1.94283823	12.7655513	2.02E-24	3.81E-21
201590_x_at	ANXA2	1.68959054	13.1436175	3.46E-24	6.31E-21
206157_at	PTX3	1.98670615	11.2102165	3.62E-24	6.38E-21
216080_s_at	FADS3	2.27239911	9.71739825	3.75E-24	6.39E-21
221463_at	CCL24	3.58807723	8.40481021	3.93E-24	6.39E-21
210427_x_at	ANXA2	1.67415609	13.1118777	3.98E-24	6.39E-21
213503_x_at	ANXA2	1.72399354	13.1135447	4.18E-24	6.51E-21
238681_at	GDPD1	2.92185146	7.19901556	4.29E-24	6.51E-21
202458_at	PRSS23	2.98100135	7.79000143	5.03E-24	7.43E-21
203761_at	SLA	1.78030673	11.2608124	6.52E-24	9.38E-21
1558397_at	---	2.20691751	9.17869031	8.35E-24	1.17E-20

214054_at	DOK2	1.67191836	12.2431311	8.80E-24	1.20E-20
228937_at	C13ORF31	2.42816683	9.90878354	9.66E-24	1.29E-20
211676_s_at	IFNGR1	1.64276331	12.0995889	1.08E-23	1.41E-20
230966_at	IL4I1	3.68319718	10.6065738	1.18E-23	1.50E-20
208816_x_at	ANXA2P2	1.61606927	11.6007732	1.33E-23	1.66E-20
204912_at	IL10RA	1.88097974	10.4596073	1.53E-23	1.83E-20
220014_at	LOC51334	3.95258058	6.49298277	1.54E-23	1.83E-20
218856_at	TNFRSF21	1.97277863	11.9973199	2.06E-23	2.40E-20
34210_at	CD52	1.74841624	11.3194919	2.57E-23	2.92E-20
211564_s_at	PDLIM4	2.13518707	9.68326105	2.72E-23	3.03E-20
223502_s_at	TNFSF13B	1.73530598	10.5512407	2.94E-23	3.21E-20
202727_s_at	IFNGR1	1.5463282	12.4669611	3.25E-23	3.48E-20
201243_s_at	ATP1B1	2.26738679	11.039008	4.33E-23	4.56E-20
209606_at	PSCDBP	2.53767762	8.05776375	4.93E-23	5.08E-20
222670_s_at	MAFB	2.65652588	11.7521547	6.27E-23	6.35E-20
223394_at	SERTAD1	1.65031524	9.76915308	6.91E-23	6.87E-20
214175_x_at	PDLIM4	1.85137891	9.80931564	8.66E-23	8.45E-20
223660_at	ADORA3	1.89720977	9.3830598	9.01E-23	8.64E-20
203217_s_at	ST3GAL5	1.78903169	9.10901818	1.17E-22	1.11E-19
204257_at	FADS3	1.78672893	9.74459459	1.23E-22	1.14E-19
223398_at	C9ORF89	1.54418891	11.0771528	1.25E-22	1.14E-19
211986_at	AHNAK	1.64967948	12.0209047	1.63E-22	1.45E-19
201278_at	DAB2	1.56823308	9.36397364	1.64E-22	1.45E-19
229797_at	MCOLN3	2.09980647	10.05118	2.01E-22	1.75E-19
202284_s_at	CDKN1A	1.789083	11.1500265	2.69E-22	2.22E-19
228579_at	---	1.73158064	8.85026747	3.40E-22	2.78E-19
204653_at	TFAP2A	1.98518712	8.32878609	5.70E-22	4.39E-19
201952_at	ALCAM	1.52577304	12.9059918	6.14E-22	4.66E-19
202087_s_at	CTSL	1.91284953	11.1924209	6.47E-22	4.84E-19
208978_at	CRIP2	1.99640335	10.1060568	6.82E-22	5.04E-19
219434_at	TREM1	1.77683606	11.1148543	6.95E-22	5.07E-19
235911_at	MFI2	1.81455526	10.1578351	7.75E-22	5.57E-19
225173_at	ARHGAP18	1.85956949	10.0159515	7.95E-22	5.65E-19
204661_at	CD52	1.6752998	11.8608631	9.08E-22	6.28E-19
202756_s_at	GPC1	1.88792383	8.93231998	9.08E-22	6.28E-19
227240_at	NGEF	1.97393626	9.35225393	9.96E-22	6.66E-19
220484_at	MCOLN3	2.10889009	9.93061659	9.98E-22	6.66E-19
214297_at	CSPG4	1.98668454	8.74794884	9.99E-22	6.66E-19
203355_s_at	PSD3	1.68707305	9.97354098	1.13E-21	7.47E-19
212386_at	---	1.80977269	8.4443852	1.22E-21	7.91E-19
201242_s_at	ATP1B1	2.36020561	10.833866	1.62E-21	1.03E-18
203760_s_at	SLA	1.76467647	10.2984296	1.71E-21	1.07E-18

204475_at	MMP1	4.89045646	6.14908101	1.97E-21	1.21E-18
228964_at	PRDM1	2.42316104	9.16116313	2.05E-21	1.24E-18
205566_at	ABHD2	1.61609464	9.56280738	2.12E-21	1.27E-18
224990_at	LOC201895	1.75486717	9.56572435	2.15E-21	1.28E-18
214830_at	SLC38A6	1.70065597	9.60777602	2.38E-21	1.38E-18
222876_s_at	CENTA2	1.62337809	9.52111995	3.45E-21	1.92E-18
218501_at	ARHGEF3	1.72054917	9.02047119	3.66E-21	2.02E-18
206134_at	ADAMDEC1	1.90734854	8.46538539	3.83E-21	2.10E-18
219385_at	SLAMF8	2.3601546	8.87175449	4.64E-21	2.49E-18
212298_at	NRP1	2.26706147	9.0154209	5.27E-21	2.77E-18
1556314_a_at	---	1.94563197	9.96244884	5.97E-21	3.05E-18
204834_at	FGL2	2.41220628	9.04212862	7.43E-21	3.63E-18
227052_at	---	1.7292497	9.65138189	8.49E-21	4.11E-18
223501_at	---	1.77755998	10.4775991	9.58E-21	4.59E-18
238669_at	PTGS1	1.79526928	9.00713066	1.52E-20	7.11E-18
203936_s_at	MMP9	1.83742157	9.54268719	2.01E-20	9.33E-18
205128_x_at	PTGS1	1.50682893	10.8982825	2.46E-20	1.12E-17
223019_at	C9ORF88	1.71440506	9.42451447	2.48E-20	1.12E-17
218223_s_at	PLEKHO1	1.76062083	9.13759715	2.55E-20	1.14E-17
226545_at	CD109	2.22747108	10.1210564	2.62E-20	1.17E-17
37145_at	GNLY	2.52474166	7.62618078	2.77E-20	1.21E-17
211661_x_at	PTAFR	1.65459655	9.40348625	3.20E-20	1.39E-17
223434_at	GBP3	1.79281477	8.94069901	5.65E-20	2.39E-17
221011_s_at	LBH /// LOC6	2.14546482	7.91354368	6.67E-20	2.79E-17
227478_at	LOC284262	2.55523487	8.16720299	7.57E-20	3.09E-17
205933_at	SETBP1	2.06852059	8.31470678	9.65E-20	3.88E-17
223126_s_at	C1ORF21	2.0098249	9.34926366	1.00E-19	3.99E-17
214255_at	ATP10A	1.87404352	8.48741153	1.17E-19	4.64E-17
203888_at	THBD	1.74251135	12.1003768	1.32E-19	5.18E-17
239761_at	GCNT1	1.60737016	9.89061934	1.78E-19	6.90E-17
205505_at	GCNT1	1.68341734	9.51667582	1.80E-19	6.93E-17
203665_at	HMOX1	2.77855009	12.0276078	1.83E-19	7.00E-17
228490_at	ABHD2	1.7612845	9.44137483	1.92E-19	7.27E-17
213428_s_at	COL6A1	1.6365876	9.11385826	2.21E-19	8.27E-17
202748_at	GBP2	2.05214857	8.5030424	2.71E-19	1.01E-16
63825_at	ABHD2	1.60237791	9.12592031	3.53E-19	1.28E-16
205542_at	STEAP1	1.7513289	7.91561507	4.15E-19	1.49E-16
215813_s_at	PTGS1	1.51668643	10.9189252	4.31E-19	1.53E-16
205891_at	ADORA2B	1.56662939	10.2505629	4.70E-19	1.66E-16
218613_at	LOC653754	1.55398123	9.29556045	4.95E-19	1.73E-16
205076_s_at	MTMR11	1.59326395	11.2341764	5.05E-19	1.76E-16
212086_x_at	LMNA	1.50357006	12.1481348	5.14E-19	1.78E-16

203104_at	CSF1R	1.64383545	11.9446038	5.33E-19	1.83E-16
228368_at	ARHGAP20	2.23117651	8.70947261	5.37E-19	1.84E-16
227889_at	AYTL1	1.59282395	10.8879284	5.43E-19	1.84E-16
203797_at	VSNL1	1.7623632	9.20419419	5.45E-19	1.84E-16
210145_at	PLA2G4A	1.69920287	9.86166848	5.50E-19	1.84E-16
220307_at	CD244	1.51030196	11.2887381	6.64E-19	2.20E-16
201280_s_at	DAB2	1.6207775	8.250618	7.03E-19	2.30E-16
205898_at	CX3CR1	1.5834422	12.3392251	7.53E-19	2.45E-16
212171_x_at	VEGF	1.67886192	11.082533	8.08E-19	2.61E-16
205419_at	EBI2	1.87963971	10.3117587	8.24E-19	2.64E-16
242794_at	MAML3	1.71070972	8.2000023	8.71E-19	2.76E-16
1553141_at	C13ORF31	2.23957531	8.21534882	9.28E-19	2.90E-16
1556034_s_at	MTMR11	1.54656669	10.734173	9.32E-19	2.90E-16
202436_s_at	CYP1B1	2.02651623	11.7446834	1.35E-18	4.08E-16
205718_at	ITGB7	1.61859456	10.0388412	1.64E-18	4.92E-16
222062_at	IL27RA	1.84145262	8.80213383	1.77E-18	5.26E-16
1565752_at	FGD2	2.03973925	8.7032554	1.80E-18	5.32E-16
203140_at	BCL6	1.6321005	9.84693758	1.88E-18	5.54E-16
209568_s_at	RGL1	1.79068455	9.03375054	2.04E-18	5.92E-16
212977_at	CXCR7	1.95857569	9.06724806	2.73E-18	7.74E-16
225809_at	DKFZP564O0	2.61498482	6.81686881	3.21E-18	8.90E-16
223723_at	MFI2	1.83918768	7.73004392	3.45E-18	9.49E-16
204141_at	TUBB2A	1.92837874	7.9645182	3.55E-18	9.72E-16
219358_s_at	CENTA2	1.61743685	10.3689956	3.67E-18	9.97E-16
218280_x_at	HIST2H2AA /	1.92645343	11.1017962	3.91E-18	1.05E-15
200884_at	CKB	1.62119168	10.3585418	3.91E-18	1.05E-15
213265_at	PGA5 /// LOC	1.54256466	9.03735387	4.18E-18	1.12E-15
228499_at	PFKFB4	1.54265427	8.78361163	4.58E-18	1.22E-15
214581_x_at	TNFRSF21	1.96726151	10.3862452	5.13E-18	1.35E-15
219256_s_at	SH3TC1	1.81211933	8.14371592	5.59E-18	1.46E-15
227134_at	SYTL1	1.63431503	10.2085878	5.74E-18	1.50E-15
210512_s_at	VEGF	1.61269337	12.1528461	5.88E-18	1.52E-15
220066_at	CARD15	1.63208119	8.81134661	6.12E-18	1.58E-15
207610_s_at	EMR2	1.96904599	7.45239164	6.31E-18	1.62E-15
225337_at	ABHD2	1.52226303	10.585684	6.47E-18	1.65E-15
1553906_s_at	FGD2	1.56817402	11.6738144	8.15E-18	2.05E-15
210757_x_at	DAB2	1.51596174	9.71603785	8.84E-18	2.22E-15
205306_x_at	KMO	1.52538689	9.01246744	1.07E-17	2.64E-15
203980_at	FABP4	2.44504844	7.91709543	1.14E-17	2.81E-15
205798_at	IL7R	2.15224639	6.90018766	1.20E-17	2.94E-15
235299_at	---	2.92455443	6.38887226	1.23E-17	2.99E-15
201422_at	IFI30	1.53617841	12.1952	1.33E-17	3.23E-15

201951_at	ALCAM	1.56151412	11.2835886	1.36E-17	3.29E-15
219412_at	RAB38	1.69022517	7.7984244	1.40E-17	3.36E-15
214290_s_at	HIST2H2AA /	1.8793137	12.5116024	1.77E-17	4.19E-15
223092_at	ANKH	1.74621066	9.31182429	1.93E-17	4.53E-15
1552553_a_at	CARD12	1.8300836	8.04038883	1.98E-17	4.61E-15
1565754_x_at	FGD2	2.05302245	8.76658914	1.98E-17	4.61E-15
1562475_at	DKFZP686O1	1.84932663	8.38987825	2.25E-17	5.18E-15
202435_s_at	CYP1B1	1.96043252	11.8853309	2.26E-17	5.18E-15
222877_at	NRP2	2.43002847	6.1162318	2.37E-17	5.41E-15
201125_s_at	ITGB5	1.55447321	9.61610321	2.48E-17	5.62E-15
204222_s_at	GLIPR1	1.64989211	10.4691144	3.30E-17	7.31E-15
1553142_at	C13ORF31	2.72312753	7.05894587	3.42E-17	7.51E-15
201279_s_at	DAB2	1.51128632	9.36621678	3.53E-17	7.64E-15
203234_at	UPP1	1.74387737	9.56780561	3.97E-17	8.52E-15
226136_at	---	1.5023264	9.021618	4.37E-17	9.27E-15
206206_at	CD180	1.61188665	9.82309399	6.95E-17	1.43E-14
212387_at	---	1.62401877	7.80816226	1.05E-16	2.07E-14
204268_at	S100A2	1.79310512	8.64238178	1.22E-16	2.38E-14
209122_at	ADFP	1.61478632	13.4092966	1.23E-16	2.41E-14
219994_at	APBB1IP	1.87740546	9.6208094	1.42E-16	2.74E-14
210095_s_at	IGFBP3	2.98798358	8.63072598	1.43E-16	2.74E-14
227948_at	FGD4	1.62553487	7.73111329	1.54E-16	2.92E-14
243483_at	TRPM8	2.13837999	7.16652124	1.62E-16	3.04E-14
212062_at	ATP9A	2.12888023	7.50745486	1.77E-16	3.29E-14
218502_s_at	TRPS1	1.61387671	8.89822927	1.95E-16	3.60E-14
213891_s_at	---	1.67207935	8.30917084	2.03E-16	3.68E-14
200878_at	EPAS1	1.51714595	9.20362299	2.04E-16	3.69E-14
201565_s_at	ID2	1.52829092	12.7810873	2.26E-16	4.06E-14
212190_at	SERPINE2	1.92452066	9.90116936	2.57E-16	4.60E-14
224480_s_at	LPAAT-THETA	1.96245654	8.74709429	2.64E-16	4.67E-14
220333_at	PAQR5	3.58344803	7.84174393	2.70E-16	4.76E-14
218589_at	P2RY5	1.65149795	9.3651465	3.00E-16	5.23E-14
225166_at	ARHGAP18	1.75622288	7.33398136	3.29E-16	5.64E-14
226066_at	MITF	1.750697	7.87439597	3.35E-16	5.73E-14
221211_s_at	C21ORF7	2.08949444	5.978895	3.41E-16	5.80E-14
225842_at	PHLDA1	2.51724542	8.55236084	3.48E-16	5.89E-14
1554992_at	RASGRF1	1.56735654	6.94135257	3.77E-16	6.35E-14
225097_at	HIPK2	1.50753986	10.7130384	3.84E-16	6.45E-14
212464_s_at	FN1	1.70809888	9.26484812	4.53E-16	7.53E-14
240076_at	---	1.5987436	8.40204375	4.66E-16	7.73E-14
203798_s_at	VSNL1	1.91644457	7.87623269	4.84E-16	7.92E-14
204575_s_at	MMP19 /// L	1.83367508	7.70439226	4.88E-16	7.96E-14

204465_s_at	INA	1.60147629	8.20221976	5.17E-16	8.36E-14
201566_x_at	ID2 /// ID2B	1.57371123	10.7833858	5.52E-16	8.87E-14
230360_at	GLDN	1.98086959	6.74193069	6.80E-16	1.07E-13
222146_s_at	TCF4	1.54556332	7.51472351	8.25E-16	1.28E-13
224341_x_at	TLR4	1.7396424	8.97197657	8.61E-16	1.32E-13
219637_at	ARMC9	1.80286893	7.06720581	8.87E-16	1.35E-13
211138_s_at	KMO	1.54711526	8.79132849	9.12E-16	1.38E-13
202437_s_at	CYP1B1	1.80921395	12.1893518	9.54E-16	1.43E-13
235458_at	HAVCR2	2.48536941	7.7122454	9.75E-16	1.46E-13
203922_s_at	CYBB	1.58449815	10.3814577	1.07E-15	1.58E-13
212143_s_at	IGFBP3	2.76854721	7.92968375	1.26E-15	1.82E-13
227716_at	UBXD5	1.51942114	9.002862	1.28E-15	1.83E-13
214211_at	FTH1	1.55999567	12.4970466	1.33E-15	1.90E-13
229004_at	---	1.51039984	9.12368109	1.55E-15	2.18E-13
202609_at	EPS8	1.5924097	8.52061192	1.82E-15	2.52E-13
217757_at	A2M	1.67532065	8.4520092	1.98E-15	2.73E-13
1552798_a_at	TLR4	1.62695353	9.04302518	2.09E-15	2.88E-13
57715_at	FAM26B	1.79873285	7.75582627	2.40E-15	3.27E-13
226282_at	---	1.60485814	9.41013847	2.84E-15	3.80E-13
222838_at	SLAMF7	1.86121844	7.05728625	3.11E-15	4.13E-13
216442_x_at	FN1	1.69780521	10.1409361	3.73E-15	4.87E-13
201324_at	EMP1	2.82050293	6.11305975	3.81E-15	4.94E-13
210264_at	GPR35	1.59109619	9.60072153	3.91E-15	5.05E-13
222858_s_at	DAPP1	1.6313133	10.6750257	4.54E-15	5.78E-13
209684_at	RIN2	2.16288563	7.25953396	5.48E-15	6.84E-13
201069_at	MMP2	1.51386957	8.69855532	6.09E-15	7.55E-13
204998_s_at	ATF5	1.63500149	10.6267979	6.14E-15	7.60E-13
202434_s_at	CYP1B1	2.2027314	9.83119314	6.94E-15	8.52E-13
205099_s_at	CCR1	1.57264838	9.76018397	7.25E-15	8.85E-13
207233_s_at	MITF	1.66865012	8.30250431	8.03E-15	9.72E-13
205552_s_at	OAS1	1.79452532	7.29881386	8.53E-15	1.02E-12
226550_at	---	1.79237731	7.77105086	9.20E-15	1.09E-12
212096_s_at	MTUS1	1.62315248	8.50418445	9.61E-15	1.13E-12
222651_s_at	TRPS1	1.5940306	10.0878238	9.64E-15	1.13E-12
211719_x_at	FN1	1.74293625	10.1007312	9.80E-15	1.15E-12
227609_at	EPSTI1	1.73531372	7.62913716	1.06E-14	1.24E-12
1558105_a_at	---	1.89855059	6.81046182	1.07E-14	1.25E-12
225207_at	PDK4	2.24881528	8.76581849	1.08E-14	1.25E-12
237160_at	CCDC83	2.26816884	5.8347316	1.15E-14	1.33E-12
211026_s_at	MGLL	1.80987658	8.99536888	1.33E-14	1.53E-12
229450_at	---	2.07979683	6.90012377	1.42E-14	1.62E-12
215602_at	FGD2	2.01984347	7.85983935	1.54E-14	1.74E-12

228708_at	RAB27B	1.75996236	8.57078526	1.63E-14	1.83E-12
210258_at	RGS13	2.4181722	5.06675503	1.77E-14	1.97E-12
210895_s_at	CD86	1.74036933	7.80363779	1.88E-14	2.07E-12
223672_at	SGIP1	1.58033388	8.69396513	1.96E-14	2.14E-12
210513_s_at	VEGF	1.62960752	9.66705476	2.08E-14	2.25E-12
212614_at	ARID5B	1.64330835	6.34592171	2.09E-14	2.26E-12
1553995_a_at	NT5E	2.06345466	6.49987213	2.17E-14	2.32E-12
233540_s_at	CDK5RAP2	1.77928193	10.6899414	2.34E-14	2.48E-12
204059_s_at	ME1	1.78078662	11.5066468	2.46E-14	2.58E-12
211527_x_at	VEGF	1.68079685	9.90807927	2.48E-14	2.60E-12
214724_at	DIXDC1	1.55892061	7.67060007	2.63E-14	2.74E-12
227556_at	NME7	2.07486651	9.31851129	2.92E-14	3.02E-12
237442_at	APBB1IP	1.97657406	7.17373032	3.09E-14	3.18E-12
224218_s_at	TRPS1	1.52587932	8.16882094	3.38E-14	3.46E-12
225188_at	RAPH1	1.90298066	6.31647018	3.68E-14	3.73E-12
244414_at	MAML2	2.39160043	8.05798482	3.70E-14	3.74E-12
209906_at	C3AR1	1.62034968	8.32122922	3.73E-14	3.76E-12
210510_s_at	NRP1	1.56055098	7.3171434	3.77E-14	3.78E-12
226629_at	SLC43A2	1.57641868	8.50211433	3.97E-14	3.94E-12
237030_at	ACPP	1.53890938	8.05225501	4.15E-14	4.10E-12
213338_at	TMEM158	1.73773739	10.7585184	4.18E-14	4.13E-12
219926_at	POPDC3	2.12181972	6.63647483	5.99E-14	5.68E-12
200897_s_at	PALLD	1.64882729	8.35346573	6.07E-14	5.74E-12
208436_s_at	IRF7	1.55075885	8.74418094	6.34E-14	5.96E-12
228438_at	TRPA1	1.65933581	10.3950167	6.81E-14	6.30E-12
227747_at	---	1.55198677	7.93194342	6.84E-14	6.32E-12
1554867_a_at	LOC51334	1.86507425	7.40812044	6.90E-14	6.36E-12
1563445_x_at	CTSLL3	1.82851184	6.84405898	9.09E-14	8.12E-12
242903_at	IFNGR1	1.7678462	7.97757472	9.49E-14	8.42E-12
229900_at	CD109	1.54089288	8.62103824	1.05E-13	9.24E-12
210495_x_at	FN1	1.61505134	10.0973935	1.07E-13	9.43E-12
218854_at	SART2	1.54263807	8.36626559	1.13E-13	9.81E-12
224989_at	---	1.78010467	7.75893731	1.17E-13	1.02E-11
238638_at	SLC37A2	1.63842433	9.93438242	1.31E-13	1.13E-11
212382_at	---	1.60505834	7.06996616	1.35E-13	1.15E-11
209047_at	AQP1	2.44653569	7.84720827	1.38E-13	1.17E-11
236345_at	TBXAS1	1.66860916	8.46774141	1.40E-13	1.18E-11
228873_at	COL22A1	1.56093003	7.43196243	1.41E-13	1.19E-11
239519_at	NRP1	2.19110297	5.55763801	1.43E-13	1.20E-11
220935_s_at	CDK5RAP2	1.84541222	10.4100106	1.54E-13	1.28E-11
1560228_at	SNAI3	1.91948596	7.8146015	1.56E-13	1.30E-11
218934_s_at	HSPB7	1.65040526	8.10534113	2.40E-13	1.90E-11

210146_x_at	LILRB2	1.9982938	6.76423766	2.86E-13	2.22E-11
209348_s_at	MAF	1.56472875	8.72338323	3.17E-13	2.42E-11
1558569_at	LOC645238	1.75050375	7.56283286	3.25E-13	2.47E-11
243856_at	---	1.73115631	8.03640769	3.81E-13	2.86E-11
223798_at	SLC41A2	1.94681117	6.54582797	3.90E-13	2.92E-11
215990_s_at	BCL6	1.50671943	8.04953142	4.81E-13	3.52E-11
202869_at	OAS1	1.63942747	6.73520018	5.30E-13	3.86E-11
225631_at	KIAA1706	1.53753899	7.78142994	5.56E-13	4.03E-11
204116_at	IL2RG	1.53970115	7.99806857	5.88E-13	4.22E-11
225189_s_at	RAPH1	1.85367315	6.14549622	6.27E-13	4.47E-11
211066_x_at	PCDHGC3 ///	1.58678656	10.4111947	7.90E-13	5.53E-11
221266_s_at	TM7SF4	1.83671444	6.22762311	8.02E-13	5.60E-11
1560485_at	HIVEP1	1.6480621	6.99003908	8.06E-13	5.62E-11
204881_s_at	UGCG	1.5102382	9.51481557	8.38E-13	5.83E-11
235286_at	CKLF	1.61741462	8.34288205	9.26E-13	6.36E-11
205003_at	DOCK4	1.5112689	8.20388936	1.02E-12	6.92E-11
218686_s_at	RHBDF1	1.51723286	7.92482272	1.05E-12	7.08E-11
221565_s_at	FAM26B	1.59642371	7.91366407	1.09E-12	7.32E-11
206675_s_at	SKIL	1.61042514	7.42083013	1.16E-12	7.69E-11
242358_at	---	2.20249712	6.04968315	1.24E-12	8.20E-11
241392_at	TMEM39A	1.61384348	7.05009494	1.87E-12	1.19E-10
232333_at	MAML2	1.68481156	8.01950459	2.06E-12	1.30E-10
228762_at	LFNG	1.55190457	9.0403074	2.08E-12	1.31E-10
242907_at	GBP2	2.14738965	6.03707956	2.72E-12	1.64E-10
203753_at	TCF4	1.50293289	7.66442858	2.78E-12	1.68E-10
207542_s_at	AQP1	1.69421791	6.82177348	3.02E-12	1.81E-10
242157_at	---	1.57383098	8.76647265	3.26E-12	1.94E-10
204058_at	ME1	1.73420796	9.51508263	3.53E-12	2.08E-10
209921_at	SLC7A11	1.94348494	9.29226579	3.63E-12	2.13E-10
211030_s_at	SLC6A6	1.51035569	7.57360907	3.78E-12	2.21E-10
209392_at	ENPP2	1.82310668	5.23034508	4.76E-12	2.73E-10
243894_at	SLC41A2	1.69547735	5.15085274	4.80E-12	2.75E-10
229937_x_at	LILRB1	1.58545389	7.41501062	5.00E-12	2.84E-10
214857_at	C10ORF95	1.60255368	7.13065345	5.02E-12	2.85E-10
230944_at	MGC45491	1.55203348	7.47887362	5.53E-12	3.14E-10
228057_at	DDIT4L	1.68290143	9.61033195	6.99E-12	3.82E-10
204105_s_at	NRCAM	2.27634648	6.95288228	7.49E-12	4.07E-10
205681_at	BCL2A1	1.64702983	9.50173198	8.19E-12	4.40E-10
242405_at	MAML2	1.86052011	7.15057318	1.10E-11	5.73E-10
217678_at	SLC7A11	1.75913555	8.8692241	1.22E-11	6.25E-10
211962_s_at	ZFP36L1	1.59912563	8.8232205	1.23E-11	6.27E-10
221060_s_at	TLR4	1.53812487	8.81340284	2.27E-11	1.08E-09

200907_s_at	PALLD	1.50739688	7.44132987	2.28E-11	1.08E-09
228918_at	SLC43A2	1.66364865	7.20166079	2.29E-11	1.09E-09
1555606_a_at	GDPD1	1.51121338	6.61034166	2.39E-11	1.13E-09
228450_at	PLEKHA7	1.50941089	6.45253703	2.70E-11	1.26E-09
229221_at	---	1.60263592	8.59003199	4.03E-11	1.79E-09
229635_at	LOC643424	1.53074512	7.55215178	4.38E-11	1.94E-09
1569149_at	PDLIM7	1.54849621	9.14969141	5.56E-11	2.41E-09
207433_at	IL10	1.52400243	5.63708634	7.49E-11	3.14E-09
221815_at	ABHD2	1.55904737	8.11542769	1.01E-10	4.08E-09
203060_s_at	PAPSS2	1.5764103	7.75963014	1.25E-10	4.94E-09
232746_at	CXCR7	2.0719893	6.54641126	1.43E-10	5.55E-09
1560960_at	MDGA1	1.97885133	5.71541524	1.47E-10	5.70E-09
234645_at	MAML2	1.87005824	6.53786268	1.72E-10	6.50E-09
223596_at	SLC12A6	1.50709112	7.32492551	1.75E-10	6.60E-09
87100_at	ABHD2	1.51939681	7.38326685	1.79E-10	6.75E-09
213931_at	ID2 /// ID2B	2.71874933	9.84931953	1.87E-10	7.02E-09
216874_at	DKFZP686O1	1.70886875	5.93467446	2.11E-10	7.76E-09
244375_at	EVL	1.56523772	7.93537524	2.24E-10	8.16E-09
1569150_x_at	PDLIM7	1.54117409	9.37943359	2.24E-10	8.18E-09
214453_s_at	IFI44	1.79674041	6.65852583	2.78E-10	9.87E-09
204999_s_at	ATF5	1.64452594	9.14215678	3.41E-10	1.18E-08
215836_s_at	PCDHGC3 ///	1.52441384	9.29079122	4.72E-10	1.60E-08
208161_s_at	ABCC3	1.61726316	8.40189868	5.05E-10	1.69E-08
202827_s_at	MMP14	1.62314882	10.2030389	5.39E-10	1.78E-08
208712_at	CCND1	1.5393933	7.40438263	6.16E-10	2.01E-08
223939_at	SUCNR1	1.57537424	8.40597144	7.17E-10	2.32E-08
205960_at	PDK4	1.69465703	7.19094792	1.28E-09	3.84E-08
214841_at	CNIH3	1.56253317	6.14111085	1.40E-09	4.15E-08
209993_at	ABCB1	1.58407983	5.06880643	1.52E-09	4.48E-08
1557938_s_at	PTRF	1.50339198	6.8700736	1.62E-09	4.73E-08
232068_s_at	TLR4	1.74396268	6.76798691	1.84E-09	5.28E-08
242321_at	---	1.6662739	6.52856887	2.12E-09	5.99E-08
219574_at	MARCH1	1.64000788	5.55000344	3.54E-09	9.43E-08
202638_s_at	ICAM1	1.58753294	6.72394157	3.76E-09	9.97E-08
219496_at	ANKRD57	1.50970429	7.47583744	4.86E-09	1.26E-07
1555756_a_at	CLEC7A	1.65932872	7.0882743	5.25E-09	1.35E-07
241929_at	CD36	1.82152709	8.32014251	5.66E-09	1.44E-07
1556423_at	VASH1	1.55220936	7.02874938	8.01E-09	1.97E-07
229435_at	GLIS3	1.5824943	4.92660385	8.07E-09	1.98E-07
217997_at	PHLDA1	2.01871208	7.37991533	8.18E-09	2.00E-07
235944_at	HMCN1	1.51434592	7.331681	9.15E-09	2.21E-07
206637_at	P2RY14	1.69022854	4.58701985	9.57E-09	2.30E-07

213293_s_at	TRIM22	1.54165851	6.59931282	9.57E-09	2.30E-07
238581_at	GBP5	1.57383447	7.67594481	1.03E-08	2.46E-07
1558404_at	LOC644242 /	1.85121181	5.31545142	1.46E-08	3.35E-07
230559_x_at	FGD4	1.51987215	5.45151267	1.69E-08	3.83E-07
1553151_at	ATP6V0D2	1.52950999	6.78084809	1.69E-08	3.84E-07
1554285_at	HAVCR2	1.64907555	7.49492704	3.00E-08	6.38E-07
244579_at	TRPS1	1.5354261	8.45494277	5.93E-08	1.16E-06
228640_at	---	1.5809974	4.58101232	7.52E-08	1.43E-06
210004_at	OLR1	1.59400178	5.26939608	8.40E-08	1.58E-06
243556_at	NGEF	1.50840974	6.73352627	1.18E-07	2.14E-06
210360_s_at	MTSS1	1.7452905	6.18923946	1.40E-07	2.49E-06
217999_s_at	PHLDA1	1.73310668	6.08679858	2.07E-07	3.52E-06
227062_at	TNCRNA	1.56840333	10.0441571	2.18E-07	3.69E-06
237904_at	ADORA3	1.52521897	6.15098521	2.49E-07	4.15E-06
1563621_at	KIAA1706	1.55572929	7.60284745	6.48E-07	9.74E-06

Downregulated:

ID	Gene	raw.FC	AveExpr	P.Value	adj.P.Val
207725_at	POU4F2	-2.8001105	9.19852692	2.12E-22	1.81E-19
212993_at	---	-1.8809512	9.86599984	2.25E-22	1.89E-19
211421_s_at	RET	-2.0125505	9.36968529	3.53E-22	2.84E-19
227899_at	VIT	-1.8754322	7.70929876	4.25E-22	3.36E-19
225224_at	C20ORF112	-2.04379	8.5964785	1.37E-21	8.79E-19
213361_at	TDRD7	-1.8488643	10.2732718	2.93E-21	1.67E-18
214539_at	SERPINB10	-2.1313083	8.01802953	3.16E-21	1.78E-18
235275_at	OXCT2	-2.0229254	12.4009174	4.06E-21	2.20E-18
203685_at	BCL2	-2.3112793	8.44431889	4.88E-21	2.59E-18
227037_at	LOC201164	-1.5468442	9.38990462	5.65E-21	2.94E-18
219714_s_at	CACNA2D3	-2.206206	9.82724428	5.72E-21	2.95E-18
206643_at	HAL	-1.9307917	9.28853464	6.18E-21	3.10E-18
211144_x_at	TRGC2 /// TR	-1.5748474	10.586818	7.12E-21	3.54E-18
217521_at	---	-1.7887534	8.38380263	7.38E-21	3.63E-18
208206_s_at	RASGRP2	-1.9706562	9.9264082	1.25E-20	5.95E-18
228977_at	IL17D	-2.1132305	7.51309566	2.19E-20	1.01E-17
209813_x_at	TRGC2 /// TR	-1.6036338	10.7697475	3.87E-20	1.65E-17
204614_at	SERPINB2	-2.3610663	10.8353035	6.10E-20	2.57E-17
212110_at	SLC39A14	-1.682778	10.5673949	7.23E-20	3.00E-17
202444_s_at	SPFH1	-1.8415073	9.34800962	7.37E-20	3.03E-17
216920_s_at	TRGC2 /// TR	-1.5704575	11.3491957	8.78E-20	3.56E-17
202441_at	SPFH1	-1.6532676	11.1411892	1.45E-19	5.66E-17

211919_s_at	CXCR4	-1.5387599	11.0738986	3.40E-19	1.25E-16
204610_s_at	CCDC85B	-1.729942	9.65009386	6.61E-19	2.20E-16
200999_s_at	CKAP4	-1.6192589	11.5934013	8.23E-19	2.64E-16
207865_s_at	BMP8B	-2.145585	9.11410521	9.38E-19	2.90E-16
217028_at	CXCR4	-1.5274428	11.5438714	1.14E-18	3.50E-16
201968_s_at	PGM1	-1.5051483	9.06546368	2.12E-18	6.10E-16
219463_at	C20ORF103	-1.5731957	10.0186106	2.55E-18	7.26E-16
212242_at	TUBA1	-1.5626324	11.2879097	2.82E-18	7.96E-16
213484_at	---	-1.5736546	8.53538561	3.16E-18	8.83E-16
209201_x_at	CXCR4	-1.5448129	11.1194624	3.16E-18	8.83E-16
218858_at	DEPDC6	-1.7866919	7.55045943	5.06E-18	1.34E-15
202236_s_at	SLC16A1	-1.5384699	10.1675739	9.26E-18	2.30E-15
208158_s_at	OSBPL1A	-1.6142678	8.3746552	1.71E-17	4.06E-15
202932_at	YES1	-1.6455703	8.57014581	2.47E-17	5.62E-15
243209_at	KCNQ4	-2.2463943	6.9665965	2.56E-17	5.79E-15
215806_x_at	TRGC2 /// TR	-1.5328764	11.0634752	3.51E-17	7.61E-15
204521_at	C12ORF24	-1.5676281	10.1844282	3.88E-17	8.36E-15
204301_at	KBTBD11	-1.5574513	10.253905	4.37E-17	9.27E-15
227920_at	KIAA1553	-1.6307063	8.01525239	5.17E-17	1.09E-14
218251_at	MID1IP1	-1.559714	9.78570246	5.29E-17	1.11E-14
212646_at	RFTN1	-1.658315	8.57843565	5.38E-17	1.12E-14
222799_at	HSPC049	-1.5489442	8.60085628	1.10E-16	2.17E-14
227103_s_at	MGC2408	-1.581709	8.7267591	1.30E-16	2.51E-14
206067_s_at	WT1	-1.511783	9.85618462	1.37E-16	2.66E-14
214369_s_at	RASGRP2	-1.5808582	9.41805033	1.69E-16	3.15E-14
206589_at	GFI1	-1.5996464	11.7281473	1.99E-16	3.65E-14
225619_at	SLAIN1	-2.2453889	7.41012008	2.01E-16	3.68E-14
212660_at	PHF15	-1.69531	8.00752875	2.63E-16	4.66E-14
218971_s_at	HSPC049	-1.5087203	9.12721477	3.08E-16	5.33E-14
201690_s_at	TPD52	-1.5492402	9.27038373	3.25E-16	5.59E-14
229638_at	IRX3	-1.6570492	11.8844594	3.38E-16	5.76E-14
223062_s_at	PSAT1	-1.556602	9.43823571	4.70E-16	7.77E-14
225510_at	OAF	-1.6632727	10.1142626	6.67E-16	1.05E-13
209485_s_at	OSBPL1A	-1.6049308	8.36910929	7.34E-16	1.15E-13
204432_at	SOX12	-1.7584476	6.5781916	8.71E-16	1.33E-13
205768_s_at	SLC27A2	-1.6303006	7.69181894	8.98E-16	1.36E-13
211576_s_at	SLC19A1	-1.5339487	9.8247482	9.81E-16	1.46E-13
201688_s_at	TPD52	-1.6048433	8.65393713	9.93E-16	1.48E-13
50314_i_at	C20ORF27	-1.561172	9.67877203	1.14E-15	1.66E-13
1553436_at	MUC19	-1.64037	7.99717726	1.18E-15	1.71E-13
202800_at	SLC1A3	-1.5176496	8.18097955	1.51E-15	2.13E-13
41037_at	TEAD4	-1.6405647	6.31029525	1.70E-15	2.36E-13

216953_s_at	WT1	-1.5276508	7.76890727	2.15E-15	2.95E-13
228055_at	NAPSB	-1.5385754	10.1648177	2.61E-15	3.52E-13
218424_s_at	STEAP3	-1.7692882	7.88028032	2.78E-15	3.74E-13
212855_at	DCUN1D4	-1.508562	7.88887861	2.92E-15	3.90E-13
202933_s_at	YES1	-1.5437793	9.12374841	3.76E-15	4.89E-13
1553138_a_at	ANKRD41	-2.0146608	6.96935627	6.26E-15	7.73E-13
227242_s_at	EBF3	-1.8363477	4.86769268	8.15E-15	9.84E-13
237265_at	C16ORF73	-1.5296704	9.74165113	9.60E-15	1.13E-12
213478_at	KIAA1026	-1.8330762	7.39399329	1.16E-14	1.34E-12
225081_s_at	CDCA7L	-1.5491727	10.2951966	1.46E-14	1.66E-12
211299_s_at	FLOT2	-1.6145204	9.10864173	1.58E-14	1.79E-12
213568_at	OSR2	-2.2462672	5.99962469	1.64E-14	1.83E-12
227662_at	SYNPO2	-1.5973696	8.62811124	1.76E-14	1.96E-12
200998_s_at	CKAP4	-1.6910951	9.77491302	2.08E-14	2.25E-12
209900_s_at	SLC16A1	-1.5885969	7.84437981	2.30E-14	2.43E-12
229084_at	CNTN4	-1.6415136	7.72735571	2.30E-14	2.43E-12
238694_at	---	-1.5762461	7.26420148	3.38E-14	3.46E-12
1555788_a_at	TRIB3	-1.5022329	9.92495817	3.64E-14	3.70E-12
221900_at	COL8A2	-1.5627579	10.2358313	4.09E-14	4.05E-12
225016_at	APCDD1	-1.6872345	6.47036912	4.21E-14	4.14E-12
225768_at	NR1D2	-1.7351352	6.8044854	5.44E-14	5.24E-12
222095_s_at	C1ORF76	-1.7301956	7.38672115	6.40E-14	6.00E-12
229103_at	WNT3	-1.7749895	5.55503782	7.97E-14	7.21E-12
205769_at	SLC27A2	-1.7824201	7.67753108	1.53E-13	1.27E-11
201689_s_at	TPD52	-1.645479	8.12663653	1.59E-13	1.31E-11
201350_at	FLOT2	-1.5079906	11.0344892	2.08E-13	1.68E-11
221648_s_at	C1ORF121	-1.517313	8.36815023	2.55E-13	2.00E-11
208078_s_at	SNF1LK	-1.597736	7.64505173	2.81E-13	2.18E-11
1562484_at	FLJ35848	-1.9050209	6.65405977	3.15E-13	2.41E-11
1555370_a_at	CAMTA1	-1.7040191	6.36041757	3.26E-13	2.47E-11
218376_s_at	MICAL1	-1.5055354	11.194367	3.44E-13	2.61E-11
204567_s_at	ABCG1	-1.8330717	5.8226155	3.51E-13	2.66E-11
39966_at	CSPG5	-1.6105172	7.68266153	4.12E-13	3.07E-11
218326_s_at	LGR4	-1.696564	6.525917	5.28E-13	3.85E-11
212430_at	RBM38	-1.5884137	8.88476901	5.78E-13	4.17E-11
227236_at	TSPAN2	-1.7695047	6.98434119	7.37E-13	5.19E-11
204794_at	DUSP2	-1.5957268	8.45706393	7.96E-13	5.57E-11
230888_at	HSPC049	-1.577802	7.20584208	9.14E-13	6.29E-11
212097_at	CAV1	-1.6628831	7.59130877	9.63E-13	6.57E-11
209353_s_at	C1ORF76	-1.7131519	7.30778535	1.02E-12	6.92E-11
201801_s_at	SLC29A1	-1.6246978	8.73200853	1.05E-12	7.08E-11
210279_at	GPR18	-1.5350315	8.98079125	1.29E-12	8.49E-11

52651_at	COL8A2	-1.577706	9.9516637	1.31E-12	8.57E-11
235758_at	PNMA6A	-1.5784572	7.86091427	1.34E-12	8.77E-11
222162_s_at	ADAMTS1	-1.842254	6.45805339	1.37E-12	8.95E-11
209369_at	ANXA3	-1.7449323	5.34631362	1.41E-12	9.18E-11
219911_s_at	SLCO4A1	-1.5143987	8.17455361	1.50E-12	9.71E-11
1557919_a_at	LOC648232	-1.5028156	12.5466889	1.73E-12	1.11E-10
219497_s_at	BCL11A	-1.5825853	9.14635109	1.85E-12	1.18E-10
232271_at	HNF4G	-1.5978388	7.3715225	2.04E-12	1.29E-10
206653_at	---	-1.5611734	6.70426513	2.13E-12	1.33E-10
225782_at	MSRB3	-1.5020089	8.17316381	2.54E-12	1.55E-10
223704_s_at	DMRT2	-1.6370445	6.61601092	5.67E-12	3.20E-10
1558613_at	OAF	-1.5776535	7.5183993	6.15E-12	3.44E-10
1555434_a_at	SLC39A14	-1.5483414	7.91388969	6.58E-12	3.65E-10
1556194_a_at	---	-1.7264827	7.80933003	1.10E-11	5.73E-10
219304_s_at	PDGFD	-1.5313053	8.14849618	1.10E-11	5.73E-10
200894_s_at	FKBP4	-1.6280907	8.06454238	1.28E-11	6.49E-10
210347_s_at	BCL11A	-1.5419287	7.82101671	1.36E-11	6.85E-10
221249_s_at	FAM117A	-1.5920148	8.42643515	1.45E-11	7.21E-10
239410_at	---	-1.521547	6.86497836	1.72E-11	8.46E-10
206039_at	RAB33A	-1.5487461	8.85562976	2.20E-11	1.05E-09
1554660_a_at	C1ORF71	-1.5203911	7.61313106	2.54E-11	1.19E-09
209776_s_at	SLC19A1	-1.5451778	7.72495148	2.90E-11	1.34E-09
1560495_at	---	-1.6478409	7.28259363	3.01E-11	1.38E-09
202234_s_at	SLC16A1	-1.5891823	7.76240785	4.97E-11	2.16E-09
207768_at	EGR4	-2.266679	5.08097601	7.18E-11	3.02E-09
207717_s_at	PKP2	-1.5155863	4.5970225	1.26E-10	4.97E-09
213912_at	KIAA0984	-1.5617265	6.49154577	1.30E-10	5.13E-09
222891_s_at	BCL11A	-1.5929549	8.42933212	2.00E-10	7.44E-09
213268_at	CAMTA1	-1.7460973	5.75010725	2.03E-10	7.52E-09
232007_at	---	-1.5199738	9.70608088	2.60E-10	9.33E-09
227099_s_at	LOC387763	-1.5087957	6.4279952	2.97E-10	1.05E-08
232614_at	BCL2	-1.6221488	7.30276639	2.99E-10	1.05E-08
222668_at	KCTD15	-1.5400712	5.79509816	3.31E-10	1.15E-08
213610_s_at	KLHL23	-1.5730988	7.2326013	4.60E-10	1.56E-08
206935_at	PCDH8	-1.6992238	5.66380311	6.65E-10	2.16E-08
203708_at	PDE4B	-1.5144333	7.44164625	8.10E-10	2.59E-08
1554298_a_at	WDR49	-1.5642625	6.77053726	8.63E-10	2.73E-08
212558_at	SPRY1	-1.6087624	5.95823849	1.41E-09	4.18E-08
242509_at	C16ORF74	-1.5318238	6.48465026	2.21E-09	6.20E-08
201939_at	PLK2	-1.5317787	7.43694803	5.43E-09	1.39E-07
242245_at	SYDE2	-1.5851454	4.93022084	5.57E-09	1.42E-07
204557_s_at	DZIP1	-1.5326546	5.01217049	5.85E-09	1.48E-07

204875_s_at	GMDS	-1.7607496	6.33236847	9.81E-09	2.35E-07
204285_s_at	PMAIP1	-1.7424137	10.9563243	1.15E-08	2.73E-07
213006_at	CEBPD	-1.9902998	8.08295825	1.47E-08	3.38E-07
1554830_a_at	STEAP3	-1.6156641	5.65856155	2.19E-08	4.84E-07
204286_s_at	PMAIP1	-1.7353429	9.45448346	6.05E-08	1.18E-06
228325_at	KIAA0146	-1.8819676	8.36526925	8.31E-08	1.57E-06
1569377_at	TMEM67	-1.9524092	4.4888277	1.11E-07	2.04E-06
242892_at	PER2	-2.1304461	6.97699912	1.72E-07	3.00E-06
1555847_a_at	LOC284454	-2.1798122	9.88866319	1.88E-07	3.24E-06

Supplementary Table 5:

Human monocyte study: pathways significantly enriched among genes significantly upregulated by Copaxone relative to mannitol at 6 hours

Pathways significantly enriched among top genes modulated by GA relative to mannitol control at 6 h:

Enriched among top downregulated genes:

Term	Pvalue	Fold Enrichm	Benjamini
GO:0007275~multicellular organismal development	6.94E-06	2.16836735	0.00270611
GO:0048731~system development	5.04E-06	2.39616613	0.00294797
GO:0048513~organ development	2.61E-06	2.76008493	0.00305609
GO:0048856~anatomical structure development	3.69E-05	2.16450216	0.00861537
GO:0030154~cell differentiation	4.49E-05	2.55555556	0.00871888
GO:0032502~developmental process	3.28E-05	1.98412698	0.00955745
GO:0003006~reproductive developmental process	8.34E-05	6.25	0.01385786
GO:0048869~cellular developmental process	0.00010797	2.41090147	0.0156803
GO:0009653~anatomical structure morphogenesis	0.00030745	2.64317181	0.03921862

Enriched among top upregulated genes:

Term	Pvalue	Fold Enrichm	Benjamini
GO:0005886~plasma membrane	1.02E-19	2.41979941	2.18E-17
GO:0031226~intrinsic to plasma membrane	1.09E-11	3.26755853	7.78E-10
GO:0016020~membrane	8.59E-12	1.53815131	9.23E-10
GO:0005887~integral to plasma membrane	2.42E-11	3.24970302	1.04E-09
GO:0044459~plasma membrane part	1.97E-11	2.40372122	1.06E-09
GO:0005576~extracellular region	1.37E-10	2.82387307	4.90E-09
GO:0031224~intrinsic to membrane	4.97E-10	1.68368379	1.53E-08
GO:0004871~signal transducer activity	1.04E-10	2.53722457	2.51E-08
GO:0060089~molecular transducer activity	1.04E-10	2.53722457	2.51E-08
GO:0004872~receptor activity	6.20E-11	2.97630615	2.99E-08
GO:0044425~membrane part	1.40E-09	1.5389803	3.75E-08
GO:0016021~integral to membrane	1.98E-09	1.67551367	4.73E-08
GO:0044421~extracellular region part	3.24E-09	3.6100505	6.97E-08
GO:0004888~transmembrane receptor activity	2.35E-09	3.76803098	3.78E-07
GO:0006955~immune response	9.81E-10	3.57048831	6.34E-07
GO:0009611~response to wounding	3.29E-10	4.09715057	6.39E-07
GO:0009605~response to external stimulus	7.26E-10	3.12728281	7.04E-07
GO:0002376~immune system process	1.92E-09	2.85245261	9.30E-07
GO:0050896~response to stimulus	2.41E-09	1.85219081	9.36E-07
GO:0032501~multicellular organismal process	7.40E-09	1.76972744	2.39E-06
GO:0050793~regulation of developmental process	3.28E-08	3.16072861	9.08E-06
GO:0009897~external side of plasma membrane	5.99E-07	6.49667519	1.17E-05
GO:0051239~regulation of multicellular organismal process	7.17E-08	2.79159385	1.54E-05
GO:0006952~defense response	6.90E-08	3.41796458	1.67E-05
GO:0006954~inflammatory response	8.72E-08	4.47517285	1.69E-05
GO:0031012~extracellular matrix	1.51E-06	5.01711743	2.70E-05
GO:0048583~regulation of response to stimulus	1.68E-07	3.61268499	2.96E-05
GO:0005578~proteinaceous extracellular matrix	2.00E-06	5.30978261	3.07E-05
GO:0009986~cell surface	1.88E-06	4.06706753	3.10E-05
GO:0002682~regulation of immune system process	3.21E-07	3.76321353	5.19E-05
GO:0005615~extracellular space	6.96E-06	3.37129055	9.98E-05
GO:0048731~system development	7.36E-07	1.9176759	0.00010967
GO:0051707~response to other organism	1.25E-06	4.4259178	0.00017294

GO:0007275~multicellular organismal development	2.71E-06	1.74240626	0.00032825
GO:0032101~regulation of response to external stimulus	2.59E-06	6.28790109	0.00033427
GO:0022610~biological adhesion	3.65E-06	2.94001057	0.00039282
GO:0007155~cell adhesion	3.47E-06	2.94838667	0.00039594
GO:0048856~anatomical structure development	4.11E-06	1.79200644	0.00041952
GO:0065008~regulation of biological quality	5.75E-06	2.06736353	0.00050661
GO:0007166~cell surface receptor linked signal transduction	5.31E-06	2.24578872	0.00051425
GO:0050727~regulation of inflammatory response	5.72E-06	8.87043189	0.00052809
GO:0006950~response to stress	6.47E-06	1.89682191	0.0005449
GO:0032502~developmental process	9.45E-06	1.64267257	0.00073237
GO:0031347~regulation of defense response	9.45E-06	5.51937984	0.0007628
GO:0009607~response to biotic stimulus	1.20E-05	3.37558639	0.00089042
GO:0019955~cytokine binding	1.09E-05	6.97096043	0.00131926
GO:0050776~regulation of immune response	2.06E-05	4.29285099	0.00147588
GO:0040011~locomotion	2.38E-05	3.21025154	0.00164377
GO:0080134~regulation of response to stress	2.54E-05	3.70014291	0.00169407
GO:0007626~locomotory behavior	3.53E-05	4.08123158	0.00227722
GO:0002684~positive regulation of immune system process	4.09E-05	4.0245478	0.00255401
GO:0000267~cell fraction	0.00027348	1.99311488	0.00366864
GO:0045028~purinergic nucleotide receptor activity, G-protein	5.12E-05	13.8685423	0.00411604
GO:0001608~nucleotide receptor activity, G-protein coupled	5.12E-05	13.8685423	0.00411604
GO:0004930~G-protein coupled receptor activity	4.66E-05	4.29264405	0.00449193
GO:0016502~nucleotide receptor activity	8.64E-05	12.5477288	0.00594437
GO:0001614~purinergic nucleotide receptor activity	8.64E-05	12.5477288	0.00594437
GO:0005626~insoluble fraction	0.00050614	2.11983643	0.00638231
GO:0048513~organ development	0.00010948	1.8456525	0.00640896
GO:0002697~regulation of immune effector process	0.00010851	6.00900225	0.00655072
GO:0051384~response to glucocorticoid stimulus	0.00011695	7.04601682	0.00664447
GO:0005624~membrane fraction	0.00064098	2.12816938	0.00762936
hsa04060:Cytokine-cytokine receptor interaction	7.88E-05	3.91086691	0.00816277
GO:0031349~positive regulation of defense response	0.00015337	6.7584243	0.00822279
GO:0048584~positive regulation of response to stimulus	0.00015308	3.78971503	0.00844122
GO:0031960~response to corticosteroid stimulus	0.00017474	6.62325581	0.00911158
GO:0042221~response to chemical stimulus	0.00023157	1.87929805	0.01115792
GO:0065007~biological regulation	0.00022752	1.23581669	0.01124356
GO:0050865~regulation of cell activation	0.00022283	4.29574375	0.01130118
GO:0048545~response to steroid hormone stimulus	0.00025981	4.21619294	0.0122074
GO:0006935~chemotaxis	0.00027256	4.65116279	0.01249951
GO:0042330~taxis	0.00027256	4.65116279	0.01249951
GO:0002703~regulation of leukocyte mediated immunity	0.0003028	7.42993441	0.01355657
GO:0002822~regulation of adaptive immune response based on	0.00034918	7.24418605	0.01492816
GO:0001568~blood vessel development	0.00034714	3.47186797	0.01517609
GO:0030154~cell differentiation	0.00037713	1.79379845	0.01576601
GO:0001944~vasculature development	0.00039042	3.42764035	0.01597268
GO:0002819~regulation of adaptive immune response	0.00040094	7.06749858	0.0160609
GO:0051241~negative regulation of multicellular organismal pro	0.0004538	4.90208078	0.01743952
GO:0051704~multi-organism process	0.00044925	2.22256907	0.01761538
GO:0007165~signal transduction	0.00048801	1.56692649	0.01837798
GO:0009617~response to bacterium	0.00051926	4.26756174	0.01917123

GO:0048519~negative regulation of biological process	0.00057125	1.62866946	0.01993331
GO:0050864~regulation of B cell activation	0.00056871	8.56455493	0.0202092
GO:0001525~angiogenesis	0.00056006	4.22401519	0.02027648
GO:0048869~cellular developmental process	0.00059519	1.73565404	0.02039329
GO:0002694~regulation of leukocyte activation	0.00064956	4.13953488	0.02184996
GO:0044243~multicellular organismal catabolic process	0.00070212	20.6976744	0.02319544
GO:0030574~collagen catabolic process	0.00070212	20.6976744	0.02319544
GO:0016477~cell migration	0.00071879	3.20321152	0.02334233
GO:0045595~regulation of cell differentiation	0.0007682	2.51728473	0.02373537
GO:0032879~regulation of localization	0.0007822	2.35870934	0.02378398
GO:0050729~positive regulation of inflammatory response	0.00076295	11.498708	0.0239569
GO:0007186~G-protein coupled receptor protein signaling path	0.00075328	2.72561968	0.0240464
GO:0051270~regulation of cell motion	0.00083518	3.6427907	0.02498336
GO:0048518~positive regulation of biological process	0.0009722	1.55920442	0.02858412
GO:0001816~cytokine production	0.00105123	7.52642706	0.0299652
GO:0007610~behavior	0.00104771	2.75968992	0.03031177
GO:0050878~regulation of body fluid levels	0.00117703	4.87004104	0.03300809
GO:0032496~response to lipopolysaccharide	0.0013154	5.68171455	0.03578575
GO:0002683~negative regulation of immune system process	0.0013154	5.68171455	0.03578575
GO:0051674~localization of cell	0.00131424	2.98966408	0.03626342
GO:0048870~cell motility	0.00131424	2.98966408	0.03626342
GO:0046903~secretion	0.00139387	3.16397571	0.03684834
GO:0006928~cell motion	0.0013811	2.46919625	0.03702169
GO:0048514~blood vessel morphogenesis	0.00142405	3.39812565	0.03712585
GO:0001501~skeletal system development	0.00146721	3.14395054	0.03772332
GO:0050867~positive regulation of cell activation	0.00151961	4.66426466	0.03853451
GO:0030247~polysaccharide binding	0.0007648	5.24382695	0.04514181
GO:0001871~pattern binding	0.0007648	5.24382695	0.04514181
GO:0004222~metalloendopeptidase activity	0.00087418	6.1483871	0.04585047
GO:0002698~negative regulation of immune effector process	0.00196103	15.0528541	0.0488232
GO:0032103~positive regulation of response to external stimulu	0.00201705	6.53610771	0.04892898
GO:0010033~response to organic substance	0.00199539	2.03004909	0.04902907

Supplementary Table 6:

Human monocyte study: probesets significantly modulated by Copaxone relative to Probioglat

Comparing GA to Probioglat (mannitol-corrected):

6 hr:

Gene	ID	raw.FC	AveExpr	t	P.Value	adj.P.Val	B
MMP9	203936_s_at	-1.292629541	9.633661421	-9.00417913	5.02E-11	2.74E-06	13.79366295
CXCL10	204533_at	-1.4567769	5.936119132	-6.81014414	4.11E-08	0.000562081	8.116620548
PRDM1	228964_at	-1.313154291	9.26923221	-6.971291607	2.48E-08	0.000562081	8.555014552
LPXN	216250_s_at	-1.187425729	11.31541598	-6.890516822	3.19E-08	0.000562081	8.335603188
FABP4	203980_at	-1.389708136	8.039221188	-6.46099351	1.24E-07	0.001003057	7.158384955
---	240076_at	-1.215498528	8.471533058	-6.450268734	1.28E-07	0.001003057	7.128790045
COL6A1	213428_s_at	-1.179979668	9.177341621	-6.522700592	1.02E-07	0.001003057	7.328492601
SLC39A8	209267_s_at	-1.140995569	10.45383427	-6.385577167	1.58E-07	0.001077715	6.950093871
MGC5618	221477_s_at	-1.161767463	10.54711794	-6.242489796	2.48E-07	0.001358427	6.553824961
SLC39A8	219869_s_at	-1.148659963	10.18771856	-6.269482421	2.28E-07	0.001358427	6.628679558
---	226218_at	-1.293734241	7.335644318	-6.105957082	3.84E-07	0.001407317	6.174562214
STEAP1	205542_at	-1.198520967	7.986105931	-6.085284096	4.10E-07	0.001407317	6.117051744
CHST11	219634_at	-1.161656277	9.510776209	-6.076431847	4.21E-07	0.001407317	6.092419333
CD9	201005_at	-1.148001473	10.9097322	-6.077437785	4.20E-07	0.001407317	6.095218657
TNFSF13B	223502_s_at	-1.137131003	10.60864679	-6.181433276	3.02E-07	0.001407317	6.384347314
LACTB	226354_at	-1.114602637	10.69691357	-6.172421261	3.10E-07	0.001407317	6.359314367
ARL6IP5	200761_s_at	-1.110895682	11.93578892	-6.064568448	4.38E-07	0.001407317	6.059402341
NFKBIE	203927_at	-1.164640934	10.05237317	-5.999749804	5.38E-07	0.001576149	5.878896428
SLIC1	228869_at	-1.12444758	10.02770092	-5.994027048	5.48E-07	0.001576149	5.862951387
MMP1	204475_at	-1.503926217	6.323535613	-5.931236098	6.69E-07	0.001741563	5.687918849
SOD2	215223_s_at	-1.203594422	9.663613978	-5.946227294	6.38E-07	0.001741563	5.729720412
NFKBIA	201502_s_at	-1.170169851	11.84159081	-5.915355343	7.04E-07	0.001748604	5.643628551
ADAMDEC1	206134_at	-1.186119869	8.53747931	-5.792799243	1.04E-06	0.002470647	5.301581782
MPEG1	226841_at	-1.141712993	9.903545974	-5.71876434	1.32E-06	0.00281664	5.094792128
ANXA2P2	208816_x_at	-1.10860736	11.64864763	-5.713084409	1.34E-06	0.00281664	5.078923724
---	244434_at	-1.284690868	6.48107186	-5.674236906	1.52E-06	0.002841091	4.970382605
CCL2	216598_s_at	-1.251679636	11.24211982	-5.665382472	1.56E-06	0.002841091	4.945640923
ISG20	204698_at	-1.21768206	6.187546743	-5.677110964	1.50E-06	0.002841091	4.978413352
MTSS1	203037_s_at	-1.213269689	11.50426359	-5.690968103	1.44E-06	0.002841091	5.017132102
IFNGR1	211676_s_at	-1.107663761	12.14804638	-5.647245873	1.65E-06	0.002912698	4.894960454
---	230795_at	-1.170214409	9.269916411	-5.633339757	1.73E-06	0.002949255	4.856100119
NFE2L3	236471_at	-1.325741532	5.264036644	-5.602644579	1.90E-06	0.003153062	4.770320239
CD36	209555_s_at	-1.141472177	9.399914183	-5.548288841	2.26E-06	0.003637419	4.618417523
CYLD	221903_s_at	-1.120730873	9.54523467	-5.504562101	2.60E-06	0.00406002	4.496226929
ICAM1	202638_s_at	-1.408492871	6.828526502	-5.488685139	2.73E-06	0.004151352	4.451863916
KIAA1505	227265_at	-1.167329255	9.931643491	-5.462371219	2.97E-06	0.004239635	4.37834442
BID	227143_s_at	-1.111208607	11.57407787	-5.471421964	2.89E-06	0.004239635	4.403630685
BID	211725_s_at	-1.101772426	11.81064935	-5.456842269	3.02E-06	0.004239635	4.362898011
IL10	207433_at	-1.278388258	5.716402855	-5.38017906	3.86E-06	0.005084082	4.148775172
ANXA2	201590_x_at	-1.106766343	13.1932317	-5.376217209	3.91E-06	0.005084082	4.137712842
TNFAIP6	206026_s_at	-1.253360437	5.465054586	-5.347128749	4.28E-06	0.005445421	4.056503503
CD14	201743_at	-1.168862821	9.563138146	-5.316275748	4.72E-06	0.005868031	3.970392966
ICAM1	202637_s_at	-1.253702992	7.707862695	-5.260277155	5.64E-06	0.006745788	3.814178371
ANXA2	210427_x_at	-1.102171109	13.1600502	-5.258189309	5.68E-06	0.006745788	3.808356221
SYNJ2	212828_at	-1.107996148	9.826612597	-5.225926873	6.29E-06	0.007311405	3.718411088
GLIPR1	226142_at	-1.147651843	8.962327278	-5.21165917	6.57E-06	0.007446185	3.678647463
ECOP	238604_at	-1.129184527	9.930482708	-5.206962339	6.67E-06	0.007446185	3.665559469
CD40	205153_s_at	-1.151666498	8.967732221	-5.187846713	7.09E-06	0.007751531	3.612302836
IFIH1	219209_at	-1.183987237	8.421660401	-5.148180801	8.03E-06	0.008613396	3.501847826
IL4I1	230966_at	-1.288614227	10.73024251	-5.103598297	9.25E-06	0.009539706	3.3777992

MAFB	218559_s_at	-1.166149832	12.50708223	-5.078302614	1.00E-05	0.010139922	3.307465174
DAB2	201278_at	-1.100253422	9.408584284	-5.070475401	1.03E-05	0.010204051	3.285709567
P2RX4	204088_at	-1.114620024	10.58041364	-5.058930244	1.06E-05	0.010392881	3.253626924
MLF1	204784_s_at	-1.162924757	9.99075341	-5.038200724	1.14E-05	0.010898965	3.196043309
STATH	206835_at	-1.221763131	10.62779253	-4.997017436	1.29E-05	0.011985435	3.081727461
GIMAP8	235306_at	-1.176939069	7.157246458	-4.953442874	1.48E-05	0.013292667	2.960906449
TATDN3	235069_at	-1.155265079	9.090917416	-4.954184877	1.48E-05	0.013292667	2.962962631
SYNJ2	216180_s_at	-1.154071911	8.135880405	-4.929194047	1.60E-05	0.013723553	2.893733825
TREM1	219434_at	-1.128003408	11.17145989	-4.927252399	1.61E-05	0.013723553	2.888357222
ANXA2	213503_x_at	-1.100387471	13.16273845	-4.89920369	1.76E-05	0.014346141	2.810722483
G0S2	213524_s_at	-1.13550056	8.756393905	-4.864241951	1.96E-05	0.01577044	2.714047757
IL10RA	204912_at	-1.119991097	10.51723794	-4.832337382	2.17E-05	0.017172678	2.62592271
BIRC3	210538_s_at	-1.257364025	4.574455867	-4.815999105	2.28E-05	0.017653285	2.580831112
NT5E	203939_at	-1.23837887	8.454605569	-4.81435914	2.29E-05	0.017653285	2.576306436
CCL5	1555759_a_at	-1.091065618	13.63611912	-4.803210314	2.37E-05	0.018024876	2.545553731
SRPX2	205499_at	-1.224512012	6.161385122	-4.767626951	2.65E-05	0.019371526	2.447484703
ARL6IP5	200760_s_at	-1.110710905	11.72044659	-4.759118084	2.72E-05	0.019594271	2.424053294
EBI3	219424_at	-1.177599648	7.063727354	-4.747406151	2.82E-05	0.019765542	2.39181393
CD40	215346_at	-1.170599513	8.770957147	-4.743900622	2.86E-05	0.019765542	2.38216714
SRA1	224130_s_at	-1.094756967	10.80273826	-4.74427031	2.85E-05	0.019765542	2.383184412
---	238501_at	-1.210558182	5.449532392	-4.739249999	2.90E-05	0.019772234	2.369371235
SLIC1	229045_at	-1.154788585	8.278985361	-4.735764605	2.93E-05	0.019772234	2.359782927
C5ORF13	238411_x_at	-1.168369423	3.799747871	-4.729714527	2.98E-05	0.01979262	2.343142335
CARD15	220066_at	-1.139368884	8.866276193	-4.727599471	3.00E-05	0.01979262	2.337325872
PLEKHO1	218223_s_at	-1.139364138	9.196171444	-4.72322624	3.05E-05	0.019825032	2.325300937
NFE2L3	204702_s_at	-1.194994547	6.870022513	-4.700190845	3.27E-05	0.020698192	2.261996607
P2RY5	218589_at	-1.17199021	9.427432429	-4.698090166	3.29E-05	0.020698192	2.256226658
PSCDBP	209606_at	-1.183385251	8.143034013	-4.694028496	3.34E-05	0.020723011	2.245071885
PTX3	206157_at	-1.132337558	11.2731131	-4.685364815	3.43E-05	0.021049395	2.22128475
GHRL	223862_at	-1.184681023	7.107227724	-4.652926559	3.79E-05	0.022520981	2.132300505
SGIP1	223672_at	-1.171379558	8.754007552	-4.655605212	3.76E-05	0.022520981	2.139643767
RPL13 /// LOC388344 /// SNORD68	214976_at	-1.149862637	6.91302234	-4.657618313	3.73E-05	0.022520981	2.145163061
C13ORF31	1553141_at	-1.224008222	8.302725201	-4.644561712	3.89E-05	0.022864548	2.109374742
---	228573_at	-1.095494796	10.19380312	-4.631832995	4.05E-05	0.023532047	2.074505369
---	213891_s_at	-1.161350542	8.369859535	-4.6072376	4.37E-05	0.02435882	2.007185862
C9ORF130	227893_at	-1.146660243	7.477719075	-4.609505841	4.34E-05	0.02435882	2.01339098
VPS33A	204590_x_at	-1.171782565	7.440638715	-4.596489396	4.51E-05	0.0246793	1.977791564
LACTB	1552486_s_at	-1.114633374	9.43978855	-4.599201582	4.48E-05	0.0246793	1.985207462
RAB27B	228708_at	-1.21461339	8.644719612	-4.589679092	4.61E-05	0.02495536	1.959174482
FXYD2	207434_s_at	-1.239113393	6.879357844	-4.572104841	4.87E-05	0.026090918	1.911160754
SOD2	216841_s_at	-1.158700223	8.295478492	-4.560165414	5.05E-05	0.026581485	1.878565314
INADL	214493_s_at	-1.187601356	5.131040605	-4.538285419	5.40E-05	0.027870856	1.818882174
BID	204493_at	-1.096232283	11.14305218	-4.540692698	5.36E-05	0.027870856	1.825445377
BTG1	240347_at	-1.15774644	6.461438165	-4.511715252	5.86E-05	0.029418338	1.746495752
CENTA2	219358_s_at	-1.132837605	10.42210942	-4.512511788	5.85E-05	0.029418338	1.748664328
LOC54103	213142_x_at	-1.132744869	10.79908168	-4.50101223	6.06E-05	0.029856835	1.71736561
---	232297_at	-1.139648276	8.459321796	-4.497720812	6.12E-05	0.029891761	1.708410798
THBD	203887_s_at	-1.086018123	12.86704089	-4.492253521	6.23E-05	0.029965807	1.693539703
KYNU	210663_s_at	-1.127340358	10.58278616	-4.473059246	6.61E-05	0.031240789	1.641366162
TATDN3	228867_at	-1.097967272	8.531934113	-4.471976681	6.63E-05	0.031240789	1.638425195
ITGB5	201125_s_at	-1.130566675	9.666825078	-4.466327905	6.74E-05	0.031516514	1.623082245
HNRPLL	225386_s_at	-1.088481025	10.99799749	-4.460762162	6.86E-05	0.031788714	1.607969562
CRYBB2	206777_s_at	-1.127374753	9.090507037	-4.448687789	7.12E-05	0.032481733	1.575200285

CD55	1555950_a_at	-1.101176032	11.04301693	-4.445571757	7.19E-05	0.032481733	1.566747173
MPEG1	226818_at	-1.102944016	9.97050985	-4.436467464	7.39E-05	0.033128758	1.542057883
POPDC3	219926_at	-1.29231542	6.734311272	-4.429606654	7.55E-05	0.033334286	1.523461118
PLAUR	214866_at	-1.119753554	10.14656188	-4.429154084	7.56E-05	0.033334286	1.522234652
MGLL	239914_at	-1.175524254	5.022630392	-4.419263125	7.79E-05	0.033549517	1.495438248
EBI2	205419_at	-1.164746574	10.37877663	-4.420900362	7.75E-05	0.033549517	1.499872746
TPSAB1 /// TPSB2 /// LOC652751	207741_x_at	-1.154419038	7.490882539	-4.420841613	7.76E-05	0.033549517	1.499713614
SLAMF8	219386_s_at	-1.160452536	10.11870418	-4.412321331	7.96E-05	0.033706051	1.47664099
VSNL1	203797_at	-1.146555642	9.264328956	-4.408028153	8.07E-05	0.033706051	1.465019636
ICAM2	213620_s_at	-1.129713999	7.807877612	-4.408303611	8.06E-05	0.033706051	1.465765192
KYNU	217388_s_at	-1.126807082	11.22411134	-4.4076297	8.08E-05	0.033706051	1.4639412
ARHGAP18	225166_at	-1.185401191	7.40195979	-4.397929651	8.32E-05	0.034459775	1.437695412
MITF	226066_at	-1.17711382	7.940535925	-4.380375333	8.78E-05	0.035783256	1.390237219
MXD1	226275_at	-1.127265535	8.586971948	-4.378277911	8.84E-05	0.035783256	1.384570238
---	241389_at	-1.132455109	7.708200396	-4.374098276	8.95E-05	0.035977233	1.373279555
EGF	206254_at	-1.227307235	5.233280125	-4.344505089	9.80E-05	0.039095287	1.293422209
MALT1	210017_at	-1.13611874	7.859166937	-4.34176347	9.88E-05	0.039138237	1.286031515
AKR1C2	211653_x_at	-1.214585987	9.21551731	-4.326149066	0.000103606	0.03933789	1.243964033
LPAAT-THETA	224480_s_at	-1.203344821	8.824024664	-4.332906163	0.000101492	0.03933789	1.262163421
MFI2	235911_at	-1.117864464	10.21327984	-4.333903075	0.000101184	0.03933789	1.264849151
ARHGAP18	225171_at	-1.101160448	10.76032616	-4.329986035	0.0001024	0.03933789	1.254297443
TXNL2	209080_x_at	-1.090564182	11.19373566	-4.32671217	0.000103428	0.03933789	1.245480376
CD55	201926_s_at	-1.087642789	11.01244539	-4.331201616	0.000102021	0.03933789	1.257571683
ADAM9	202381_at	-1.128877619	10.06845302	-4.279524934	0.000119414	0.044617568	1.118609331
OSBPL11	218304_s_at	-1.120096667	8.80861724	-4.268337994	0.000123545	0.044617568	1.08859065
C5ORF32	224707_at	-1.108842364	9.601741209	-4.267644263	0.000123806	0.044617568	1.086729874
CD300A	209933_s_at	-1.091909319	11.06824601	-4.277981771	0.000119976	0.044617568	1.114467084
ATP2C1	237278_x_at	-1.125200201	4.516837003	-4.260468127	0.000126535	0.044741242	1.067486814
TGM5	207911_s_at	-1.09857286	10.99738367	-4.255457996	0.000128475	0.044741242	1.054057681
CAST	208908_s_at	-1.095838812	10.46135517	-4.255714901	0.000128375	0.044741242	1.054746174
TNFRSF9	207536_s_at	-1.166941138	6.648005871	-4.24598261	0.000132224	0.045183472	1.028672831
HMGB2	243368_at	-1.1602025	4.887163856	-4.246316908	0.00013209	0.045183472	1.029568135
TNFAIP3	202644_s_at	-1.125318693	10.64905332	-4.248463459	0.000131232	0.045183472	1.035317461
C1ORF21	223125_s_at	-1.110154297	11.06582035	-4.239901855	0.000134686	0.045738952	1.012391265
---	212387_at	-1.148178981	7.864705793	-4.224551183	0.000141103	0.047622271	0.971320465

12 hr:

Gene	ID	raw.FC	AveExpr	t	P.Value	adj.P.Val	B
PRDM1	228964_at	-1.313118696	7.671112637	-8.624602424	1.41E-10	7.72E-06	11.30481407
RCSD1	239328_at	-1.291780388	9.915396708	-6.452107966	1.22E-07	0.0033307	6.314951985
BTG1	240347_at	-1.25621874	6.635169562	-5.704711191	1.33E-06	0.024224991	4.462099081
FBXO45	225099_at	1.133507908	9.692476262	5.519583628	2.40E-06	0.032821958	3.997791459
ZNF566	240239_at	1.209024056	6.202067445	5.352167742	4.09E-06	0.044773508	3.577071138

24 hr:

Gene	ID	raw.FC	AveExpr	t	P.Value	adj.P.Val	B
MMP9	203936_s_at	-1.258783748	8.76550502	-6.630884212	7.89E-08	0.00431641	6.037284204

Supplementary Table 7:

Human monocyte study: pathways significantly enriched among genes significantly upregulated by Probioglat relative to Copaxone at 6 hours

Category	Term	Pathway	Fold Enrichm	PValue
KEGG_PATHWAY	hsa04060	Cytokine-cytokine receptor interaction	4.35698707	1.27E-04
KEGG_PATHWAY	hsa04621	NOD-like receptor signaling pathway	10.0427913	2.62E-04
GO_BP	GO:0002237	response to molecule of bacterial origin	13.5313828	1.85E-06
GO_BP	GO:0006955	immune response	3.79467041	3.41E-06
GO_BP	GO:0042981	regulation of apoptosis	3.43754347	6.44E-06
GO_BP	GO:0043067	regulation of programmed cell death	3.40367604	7.38E-06
GO_BP	GO:0010941	regulation of cell death	3.39114717	7.77E-06
GO_BP	GO:0009611	response to wounding	4.1168594	1.28E-05
GO_BP	GO:0032496	response to lipopolysaccharide	13.2238514	1.35E-05
GO_BP	GO:0045428	regulation of nitric oxide biosynthetic process	26.9374751	3.12E-05
GO_BP	GO:0002684	positive regulation of immune system process	6.1118641	3.39E-05
GO_BP	GO:0002822	regulation of adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains	15.8686217	3.47E-05
GO_BP	GO:0002819	regulation of adaptive immune response	15.5852535	3.79E-05
GO_BP	GO:0060341	regulation of cellular localization	5.86541797	4.67E-05
GO_BP	GO:0050878	regulation of body fluid levels	8.25318386	4.82E-05
GO_BP	GO:0006952	defense response	3.54786258	6.58E-05
GO_BP	GO:0051046	regulation of secretion	6.48099649	6.85E-05
GO_BP	GO:0042127	regulation of cell proliferation	3.14213496	7.26E-05
GO_BP	GO:0006916	anti-apoptosis	6.35515189	7.86E-05
GO_BP	GO:0051223	regulation of protein transport	8.93189964	1.24E-04
GO_BP	GO:0043066	negative regulation of apoptosis	4.52001701	1.42E-04
GO_BP	GO:0001775	cell activation	5.06837511	1.43E-04
GO_BP	GO:0043069	negative regulation of programmed cell death	4.45706413	1.59E-04
GO_BP	GO:0060548	negative regulation of cell death	4.44468339	1.63E-04
GO_BP	GO:0042113	B cell activation	11.483871	1.65E-04
GO_BP	GO:0070201	regulation of establishment of protein localization	8.41517817	1.72E-04
GO_BP	GO:0046903	secretion	4.84874552	1.99E-04
GO_BP	GO:0009617	response to bacterium	6.02952811	3.40E-04
GO_BP	GO:0010033	response to organic substance	3.02626281	3.46E-04
GO_BP	GO:0032880	regulation of protein localization	7.37852579	3.51E-04
GO_BP	GO:0006954	inflammatory response	4.4757651	3.60E-04
GO_BP	GO:0045429	positive regulation of nitric oxide biosynthetic process	27.7071173	3.70E-04
GO_BP	GO:0002706	regulation of lymphocyte mediated immunity	13.4687376	4.89E-04
GO_BP	GO:0051249	regulation of lymphocyte activation	6.87997675	5.10E-04
GO_BP	GO:0051251	positive regulation of lymphocyte activation	8.9976721	5.13E-04
GO_BP	GO:0002697	regulation of immune effector process	8.64132865	6.18E-04
GO_BP	GO:0050708	regulation of protein secretion	12.5398591	6.42E-04
GO_BP	GO:0032101	regulation of response to external stimulus	6.40400352	7.44E-04
GO_BP	GO:0002696	positive regulation of leukocyte activation	8.23371881	7.70E-04
GO_BP	GO:0002703	regulation of leukocyte mediated immunity	11.9231447	7.77E-04
GO_BP	GO:0051050	positive regulation of transport	5.21838083	8.05E-04
GO_BP	GO:0007155	cell adhesion	2.90924731	8.70E-04
GO_BP	GO:0051047	positive regulation of secretion	8.00710269	8.73E-04
GO_BP	GO:0051241	negative regulation of multicellular organismal process	6.20875951	8.74E-04
GO_BP	GO:0022610	biological adhesion	2.90509717	8.81E-04
GO_BP	GO:0030888	regulation of B cell proliferation	20.7803379	8.82E-04

GO_BP	GO:0002694	regulation of leukocyte activation	6.13395518	9.31E-04
GO_BP	GO:0050867	positive regulation of cell activation	7.86283057	9.48E-04
GO_BP	GO:0048584	positive regulation of response to stimulus	4.93092765	0.00112022
GO_BP	GO:0030097	hemopoiesis	4.93092765	0.00112022
GO_BP	GO:0032680	regulation of tumor necrosis factor production	18.7693375	0.00119195
GO_BP	GO:0050865	regulation of cell activation	5.81849462	0.00122343
GO_BP	GO:0045321	leukocyte activation	4.80867324	0.00129524
GO_BP	GO:0051173	positive regulation of nitrogen compound metabolic process	2.9363521	0.00135277
GO_BP	GO:0051240	positive regulation of multicellular organismal process	4.76925789	0.00135811
GO_BP	GO:0001817	regulation of cytokine production	5.62561635	0.00145409
GO_BP	GO:0050727	regulation of inflammatory response	9.56989247	0.00176885
GO_BP	GO:0010647	positive regulation of cell communication	3.97921365	0.00177694
GO_BP	GO:0002250	adaptive immune response	9.44560816	0.00185618
GO_BP	GO:0002460	adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains	9.44560816	0.00185618
GO_BP	GO:0051384	response to glucocorticoid stimulus	9.32451061	0.00194645
GO_BP	GO:0048534	hemopoietic or lymphoid organ development	4.4757651	0.00195153
GO_BP	GO:0048545	response to steroid hormone stimulus	5.30331541	0.00196163
GO_BP	GO:0006959	humoral immune response	9.20647883	0.00203972

Supplementary Table 8:

Genes significantly modulated by Copaxone treatment in all three studies.

The table shows the expression level of each gene as modulated by Copaxone compared to baseline (human PBMC), mannitol (human monocyte) or medium (mouse splenocytes). Although some genes are significantly differentially expressed in the same direction across all compartments and systems, other genes are modulated differently across the different systems. This shows that Copaxone may induce pathways or cell types differently depending on a given experimental setup and a well-designed genome-wide assay is required to ascertain mechanism and effect of Copaxone. Starred genes did not meet effect size cutoff of 0.5 employed in human PBMC study for conducting enrichments.

Gene	Direction in human PBMC (Copaxone relative to Baseline)	Direction in human monocytes (Copaxone relative to Mannitol)	Direction in mouse splenocytes (Copaxone relative to Medium)
ABCF2	DOWN	DOWN	UP
ABI2	UP	UP	UP
ACP6	DOWN	DOWN	DOWN
AFG3L2	DOWN	DOWN	UP
ALMS1	DOWN	UP	UP
ARPC4	UP	UP	UP
CALM3	UP	DOWN	DOWN
CCDC64	UP	DOWN	DOWN
CD84	UP	UP	DOWN
CDC6	UP	DOWN	UP
CHAF1A	DOWN	DOWN	UP
CLU	UP	UP	DOWN
COX11	DOWN	DOWN	UP
DLGAP1	DOWN	UP	DOWN
DTX4	DOWN	UP	DOWN
FAM49B	DOWN	UP	UP
FHL1	UP	DOWN	DOWN
FNTB	UP	DOWN	DOWN
GYPC	UP	DOWN	DOWN
HFE	UP	UP	UP
IL10*	UP	UP	UP
LPHN1	DOWN	DOWN	DOWN
NACA*	DOWN	DOWN	UP
OLAH	DOWN	DOWN	UP
PATZ1	UP	DOWN	DOWN
PDK1	UP	DOWN	DOWN
POLI	DOWN	DOWN	DOWN
REEP5	DOWN	UP	DOWN
RPL5*	DOWN	UP	DOWN
RPS6KA2	DOWN	UP	DOWN
SEC31A	DOWN	DOWN	DOWN
SETBP1	DOWN	UP	DOWN
SNRPA1	DOWN	DOWN	UP
SYNCRIP	DOWN	DOWN	DOWN
TNFSF9	DOWN	DOWN	UP
TOMM40	DOWN	DOWN	UP
TPM1	UP	DOWN	DOWN
TSHZ1*	DOWN	DOWN	DOWN
TSPAN13	DOWN	DOWN	DOWN
UBAP2	DOWN	DOWN	UP
VAV3	DOWN	UP	DOWN
VDAC2	DOWN	DOWN	UP
ZFAND6	DOWN	UP	DOWN

Supplementary Figure 1:

Levels of Copaxone measured over time in cell culture medium

Copaxone concentration in medium over time remains steady in the range of 44-52 µg/mL over 24 hours.

