

HEPATITIS C VIRUS INFECTION BIOMARKERS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Application Serial No. 60/795,520, filed on April 26, 2006. The disclosure of the prior application is considered part of (and is
5 incorporated by reference in) the disclosure of this application.

TECHNICAL FIELD

This invention relates to hepatitis C virus (HCV) infection, and more particularly to a signature set of HCV infection.

BACKGROUND

10 Infection by hepatitis C virus ("HCV") is a compelling human medical problem. HCV is recognized as the causative agent for most cases of non-A, non-B hepatitis, with an estimated human sero-prevalence of 3% globally (A. Alberti *et al.*, "Natural History of Hepatitis C," (1999) *J. Hepatology*, 31, (Suppl. 1), pp. 17-24). Nearly four million
15 individuals may be infected in the United States alone (M.J. Alter *et al.*, "The Epidemiology of Viral Hepatitis in the United States," (1994) *Gastroenterol. Clin. North Am.*, 23, pp. 437-455; M. J. Alter "Hepatitis C Virus Infection in the United States," (1999) *J. Hepatology*, 31, (Suppl. 1), pp. 88-91).

Upon first exposure to HCV only about 20% of infected individuals develop acute clinical hepatitis while others appear to resolve the infection spontaneously. In almost
20 70% of instances, however, the virus establishes a chronic infection that persists for decades (S. Iwarson, "The Natural Course of Chronic Hepatitis," (1994) *FEMS Microbiology Reviews*, 14, pp. 201-204; D. Lavanchy, "Global Surveillance and Control of Hepatitis C," (1999) *J. Viral Hepatitis*, 6, pp. 35-47). This usually results in recurrent and progressively worsening liver inflammation, which often leads to more severe
25 disease states such as cirrhosis and hepatocellular carcinoma (M.C. Kew, "Hepatitis C and Hepatocellular Carcinoma", (1994) *FEMS Microbiology Reviews*, 14, pp. 211-220; I. Saito *et. al.*, "Hepatitis C Virus Infection is Associated with the Development of

Hepatocellular Carcinoma,” (1990) *Proc. Natl. Acad. Sci. USA*, 87, pp. 6547-6549). It is estimated that HCV infects 170 million persons worldwide. Over the next ten years, as a larger proportion of patients who are currently infected enter the third decade of their infection, the number of deaths attributed to hepatitis C is expected to significantly increase. Unfortunately, there are no broadly effective treatments for the debilitating progression of chronic HCV.

SUMMARY

The inventors have identified a set of genes, e.g., a signature set, associated with HCV infection. The inventors have also determined that the anti-viral activity of VX-950 results in changes in gene expression, e.g., treatment with VX-950 leads to normalization of the signature set such that the gene transcript levels after 14 days of treatment more closely resemble levels seen in non-infected subjects. Further, the inventors have established a baseline gene expression set which includes genes, e.g., interferon-sensitive genes (ISGs) that can be monitored and correlated with (and optionally, predictive of) treatment, e.g., VX-950 dosing, outcomes.

In one aspect, the disclosure features a method of evaluating a subject (e.g., a subject suspected of having a viral infection, e.g., HCV infection), e.g., for the presence or level of hepatitis C virus (HCV) infection (e.g., chronic HCV). The method includes providing an evaluation of the expression of the genes in a signature set of genes in the subject, wherein the signature set has the following properties: it includes a plurality of genes each of which is differentially expressed as between virally infected individuals and non-infected individuals and it contains a sufficient number of differentially expressed genes such that differential expression (e.g., as compared to a non-infected reference) of each of the genes in the signature set in a subject is predictive of infection with no more than about 15, about 10, about 5, about 2.5, or about 1% false positives (wherein false positive means identifying a subject as virus infected when the subject is not infected); and providing a comparison of the expression of each of the genes in the set from the subject with a reference value, thereby evaluating the subject.

In some embodiments, the comparison includes comparing expression in the subject with a non-infected reference and wherein differential expression of each of the

genes in the signature set of genes indicates, a first state, e.g., infection or a first likelihood of infection, and differential expression of less than all of the genes in the signature set indicates a second state, e.g., non-infection or a second likelihood of infection.

5 In some embodiments, the reference is a value of expression from one or more, e.g., a cohort of, uninfected subjects.

 In some embodiments, the comparison includes comparing the expression in the subject with an infected reference and wherein non-differential (e.g., similar) expression of each of the genes in the signature set of genes indicates a first state, e.g., infection or a first likelihood of infection, and non-differential (e.g., similar) expression of less than all of the genes in the signature set indicates a second state, e.g., non-infection or a second likelihood of infection.

 In some embodiments, the reference is a value of expression from one or more, e.g., a cohort of, virally infected subjects.

15 In some embodiments, peripheral blood from the subject is evaluated.

 In some embodiments, the evaluating occurs prior to administering an inhibitor of a viral protease to the subject.

 In other embodiments, the evaluating occurs during the course of administering or after administering an inhibitor of a viral protease to the subject (optionally in combination with evaluating prior to administering the inhibitor).

20 In some embodiments, the inhibitor is VX-950, SCH-503034, or BILN-261 (ciluprevir).

 In some embodiments, the method includes determining a post administration level of gene expression, determined, e.g., at the RNA or protein level, for an interferon sensitive gene (ISG) in the subject to provide a post administration determined value; and comparing the post administration determined value with a reference value, (by way of example, the reference value can be the level of expression of the ISG prior to administration of the antiviral treatment), thereby evaluating the subject, e.g., determining if the subject is an enhanced responder or a non-enhanced responder.

30 In some embodiments, the method includes determining a pre administration level of gene expression, determined, e.g., at the RNA or protein level, for an interferon

sensitive gene (ISG) in the subject to provide a pre administration determined value; and comparing the pre administration determined value with a reference value, (by way of example, the reference value can be the level of expression of the ISG after commencing administration of the antiviral treatment), thereby evaluating the subject, e.g.,

5 determining if the subject is an enhanced responder or a non-enhanced responder.

In some embodiments, the signature set of genes includes a plurality of genes associated with hepatitis C virus (HCV) infection (e.g., chronic infection). In some embodiments, the signature set of genes includes a plurality of genes listed in Table 2. In some embodiments, the signature set of genes includes at least about 10%, about 20%,
10 about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 96%, about 97%, about 98, or about 99% of the genes listed in Table 2.

In some embodiments, the signature set of genes includes a gene from one or more, e.g., each of the following categories (e.g., ontology categories): organismal physiological processes; immune response (e.g., IFIT2, IFIT3, IFIT4, IFI5, IFI16, IFI27,
15 IFI30, IFI35, IFI44, IFITM1, IFITM2, IFITM3, MX1); defense response (e.g., ITGB1); response to biotic stimulus (e.g., CCR1); response to stimulus (e.g., OGG1); response to stress (e.g., CEBP/B); response to pest, pathogen, or parasite (e.g., IFI27); or response to virus (e.g., IRF7, PLSCR1). In some embodiments, the signature set of genes includes a gene from each of 2, 3, 4, 5, 6, 7, or 8 gene ontology categories described herein. In
20 some embodiments, the signature set of genes includes a plurality of genes from each of 2, 3, 4, 5, 6, 7, or 8 gene ontology categories described herein.

In some embodiments, the signature set of genes includes one or more interferon-sensitive genes (ISG). In some embodiments, the ISG is selected from the group consisting of: IFIT1, RSAD2, IFIT2, IFI16, IFI44, IFIT2, IFIT5, PLSCR1, IFIT3, IFI35,
25 IFITM1, IFITM3, IFI30, IFITM1, IFITM2, GIP2, OAS3, IFIT3, MX1, IFIL44L, IFI27, IFIT2A, PRSAD, or IFITA. In some embodiments, the signature set of genes includes at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or all of: GIP2, OAS3, IFIT3, MX1, IFIL44L, PLSCR1, IFI27, IFIT2A, PRSAD, or IFITA.

In some embodiments, the signature set of genes includes at least 20, 40, 60, 80,
30 100, 150, or 200 genes.

In other embodiments, the signature set of genes includes no more than 20, 40, 60, 80, 100, 150, or 200 genes.

In some embodiments, the signature set of genes includes the genes listed in Table 2.

5 In some embodiments, the signature set of genes includes at least 10, 20, 30, 40, or 50 genes which are more highly expressed in infection than in non infection.

In other embodiments, the signature set of genes includes at least 10, 20, 30, 40, or 50 genes which are more highly expressed in non-infection than in infection.

10 In some embodiments, the method includes assigning the subject to a diagnostic class.

In some embodiments, the method includes selecting the subject for a treatment.

In some embodiments, the method further includes providing the evaluation to the subject, a third party payer, an insurance company, employer, employer sponsored health plan, HMO, governmental entity, healthcare provider, a treating physician, an HMO, a
15 hospital, an entity which sells or supplies a drug.

In one aspect, the disclosure features a method of evaluating the efficacy of a treatment of HCV infection (e.g., chronic HCV) in a subject. The method includes administering the treatment; and performing an evaluation described herein, thereby
20 evaluating the efficacy of the treatment.

In some embodiments, the method includes providing a determination of a first level of gene expression associated with HCV infection in the subject at a first time point (e.g., wherein the first time point is prior to, or within about 1, 2, 3, 4, or 5 days of the commencement of, administration of an anti-HCV therapy (e.g., an HCV protease
25 inhibitor, e.g., VX-950)); providing a determination of a second level of gene expression in the subject at a second time point after the first time point and preferably the second time point is after commencement of administration of anti-HCV therapy (e.g., wherein the second time point is taken at least 1, 2, 3, 4, 5, or more days after the first time point or wherein the second time point is 7, 8, 9, 10, 11, 12, 13, 14 or more days after the
30 commencement of administration of the anti-HCV therapy); and providing a comparison of the first and second levels of gene expression, wherein sustained levels of gene

expression (e.g., the levels differ by no more than about 60%, about 50%, about 40%, about 30%, about 20%, about 10%, about 5%, about 2%, or about 1%) between the first and second time points is indicative of effective treatment.

In some embodiments, providing a comparison of the first and second levels of gene expression includes a comparison of the levels of one or more interferon-sensitive genes (ISG). In some embodiments, the ISG is selected from the group consisting of: IFIT1, RSAD2, IFIT2, IFI16, IFI44, IFIT2, IFIT5, PLSCR1, IFIT3, IFI35, IFITM1, IFITM3, IFI30, IFITM1, IFITM2, GIP2, OAS3, IFIT3, MX1, IFIL44L, IFI27, IFIT2A, PRSAD, or IFITA. In some preferred embodiments, first and second levels of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or all of: GIP2, OAS3, IFIT3, MX1, IFIL44L, PLSCR1, IFI27, IFIT2A, PRSAD, or IFITA are compared.

In another aspect, the disclosure features a method of evaluating the efficacy of a treatment of HCV infection (e.g., chronic HCV) in a subject. The method includes providing a determination of a first level of gene expression associated with HCV infection in the subject at a first time point (e.g., wherein the first time point is prior to, or within about 1, 2, 3, 4, or 5 days of the commencement of, administration of an anti-HCV therapy (e.g., an HCV protease inhibitor, e.g., VX-950)); providing a determination of a second level of gene expression in the subject at a second time point after the first time point and preferably the second time point is after commencement of administration of anti-HCV therapy (e.g., wherein the second time point is taken at least 1, 2, 3, 4, 5, or more days after the first time point or wherein the second time point is 7, 8, 9, 10, 11, 12, 13, 14 or more days after the commencement of administration of the anti-HCV therapy); and providing a comparison of the first and second levels of gene expression to a control level of gene expression, wherein a smaller difference between the second level and the control level as compared to the difference between the first level and the control level is indicative of effective treatment.

In some embodiments, the control corresponds to the level in a non-HCV infected subject or in a cohort of non-infected subjects.

In another aspect, the disclosure features a method of evaluating the efficacy of a drug for use in treatment of HCV infection (e.g., chronic HCV) in a subject. The method includes providing a determination of a first level of gene expression associated with HCV infection in the subject at a first time point (e.g., wherein the first time point is prior to, or within about 1, 2, 3, 4, or 5 days of the commencement of, administration of an anti-HCV therapy (e.g., an HCV protease inhibitor, e.g., VX-950)); providing a determination of a second level of gene expression in the subject at a second time point after the first time point and preferably the second time point is after commencement of administration of anti-HCV therapy (e.g., wherein the second time point is taken at least 1, 2, 3, 4, 5, or more days after the first time point or wherein the second time point is 7, 8, 9, 10, 11, 12, 13, 14 or more days after the commencement of administration of the anti-HCV therapy); and providing a comparison of the first and second levels of gene expression, wherein sustained levels of gene expression (e.g., the levels differ by no more than about 60%, about 50%, about 40%, about 30%, about 20%, about 10%, about 5%, about 2%, or about 1%) between the first and second time points is indicative of drug efficacy.

In some embodiments, the comparison of the first and second levels of gene expression includes comparing the levels of one or more interferon-sensitive genes (ISG). In some embodiments, the ISG is selected from the group consisting of: IFIT1, RSAD2, IFIT2, IFI16, IFI44, IFIT2, IFIT5, PLSCR1, IFIT3, IFI35, IFITM1, IFITM3, IFI30, IFITM1, IFITM2, GIP2, OAS3, IFIT3, MX1, IFIL44L, IFI27, IFIT2A, PRSAD, or IFITA. In some preferred embodiments, first and second levels of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or all of: GIP2, OAS3, IFIT3, MX1, IFIL44L, PLSCR1, IFI27, IFIT2A, PRSAD, or IFITA are compared.

In another aspect, the disclosure features a method of evaluating the efficacy of a drug for use in treatment of HCV infection (e.g., chronic HCV) in a subject. The method includes providing a determination of a first level of gene expression associated with HCV infection in the subject at a first time point (e.g., wherein the first time point is prior to, or within about 1, 2, 3, 4, or 5 days of the commencement of, administration of an anti-HCV therapy (e.g., an HCV protease inhibitor, e.g., VX-950)); providing a

determination of a second level of gene expression in the subject at a second time point after the first time point and preferably the second time point is after commencement of administration of anti-HCV therapy (e.g., wherein the second time point is taken at least 1, 2, 3, 4, 5, or more days after the first time point or wherein the second time point is 7,
5 8, 9, 10, 11, 12, 13, 14 or more days after the commencement of administration of the anti-HCV therapy); and providing a comparison of the first and second levels of gene expression to a control level of gene expression, wherein a smaller difference between the second level and the control level as compared to the difference between the first level and the control level is indicative of drug efficacy.

10 In some embodiments, the gene expression associated with HCV infection is determined for a plurality of the genes listed in Table 2.

In some embodiments, the plurality includes at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 96%, about 97%, about 98, or about 99% of the genes listed in Table 2. In some
15 embodiments, the plurality includes the genes listed in Table 2.

In some embodiments, the plurality includes a gene from one or more, e.g., each of the following categories (e.g., ontology categories): organismal physiological processes; immune response (e.g., IFIT2, IFIT3, IFIT4, IFI5, IFI16, IFI27, IFI30, IFI35, IFI44, IFITM1, IFITM2, IFITM3, MX1); defense response (e.g., ITGB1); response to
20 biotic stimulus (e.g., CCR1); response to stimulus (e.g., OGG1); response to stress (e.g., CEBP/B); response to pest, pathogen, or parasite (e.g., IFI27); or response to virus (e.g., IRF7, PLSCR1). In some embodiments, the plurality includes a gene from each of 2, 3, 4, 5, 6, 7, or 8 gene ontology categories described herein. In some embodiments, the plurality includes a plurality of genes from each of 2, 3, 4, 5, 6, 7, or 8 gene ontology
25 categories described herein.

In another aspect, the disclosure features a method of monitoring treatment for HCV infection (e.g., chronic HCV) in a subject and includes administering the treatment (e.g., a treatment described herein), performing an evaluation described herein, thereby
30 monitoring the treatment.

In some embodiments, the method includes providing a determination of a first level of gene expression associated with HCV infection in the subject at a first time point (e.g., wherein the first time point is prior to, or within about 1, 2, 3, 4, or 5 days of the commencement of, administration of an anti-HCV therapy (e.g., an HCV protease inhibitor, e.g., VX-950)); providing a determination of a second level of gene expression in the subject at a second time point after the first time point and preferably the second time point is after commencement of administration of anti-HCV therapy (e.g., wherein the second time point is taken at least 1, 2, 3, 4, 5, or more days after the first time point or wherein the second time point is 7, 8, 9, 10, 11, 12, 13, 14 or more days after the commencement of administration of the anti-HCV therapy); providing a comparison of the first and second levels of gene expression; and providing a determination of whether levels of gene expression are sustained (e.g., the levels differ by no more than about 60%, about 50%, about 40%, about 30%, about 20%, about 10%, about 5%, about 2%, or about 1%) between the first and second time points, thereby monitoring the treatment.

In some embodiments, the comparison of the first and second levels of gene expression includes comparing the levels of one or more interferon-sensitive genes (ISG). In some embodiments, the ISG is selected from the group consisting of: IFIT1, RSAD2, IFIT2, IFI16, IFI44, IFIT2, IFIT5, PLSCR1, IFIT3, IFI35, IFITM1, IFITM3, IFI30, IFITM1, IFITM2, GIP2, OAS3, IFIT3, MX1, IFIL44L, IFI27, IFIT2A, PRSAD, or IFITA. In some preferred embodiments, first and second levels of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or all of: GIP2, OAS3, IFIT3, MX1, IFIL44L, PLSCR1, IFI27, IFIT2A, PRSAD, or IFITA are compared.

In another aspect, the disclosure features a method of monitoring treatment for HCV infection (e.g., chronic HCV) in a subject. The method includes providing a determination of a first level of gene expression associated with HCV infection in the subject at a first time point (e.g., wherein the first time point is prior to, or within about 1, 2, 3, 4, or 5 days of the commencement of, administration of an anti-HCV therapy (e.g., an HCV protease inhibitor, e.g., VX-950)); providing a determination of a second level of gene expression in the subject at a second time point after the first time point and preferably the second time point is after commencement of administration of anti-HCV

therapy (e.g., wherein the second time point is taken at least 1, 2, 3, 4, 5, or more days after the first time point or wherein the second time point is 7, 8, 9, 10, 11, 12, 13, 14 or more days after the commencement of administration of the anti-HCV therapy); and providing a comparison of the first and second levels of gene expression to a control level of the gene transcript, thereby monitoring the treatment.

In some embodiments, the gene expression associated with HCV infection is determined for a plurality of the genes listed in Table 2. In some embodiments, the plurality includes at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 96%, about 97%, about 98, or about 99% of the genes listed in Table 2. In some embodiments, the plurality includes the genes listed in Table 2.

In some embodiments, the plurality includes a gene from one or more, e.g., each of the following categories (e.g., ontology categories): organismal physiological processes; immune response (e.g., IFIT2, IFIT3, IFIT4, IFI5, IFI16, IFI27, IFI30, IFI35, IFI44, IFITM1, IFITM2, IFITM3, MX1); defense response (e.g., ITGB1); response to biotic stimulus (e.g., CCR1); response to stimulus (e.g., OGG1); response to stress (e.g., CEBP/B); response to pest, pathogen, or parasite (e.g., IFI27); or response to virus (e.g., IRF7, PLSCR1).

In some embodiments, the plurality comprises a gene from each of 2, 3, 4, 5, 6, 7, or 8 gene ontology categories described herein.

In one aspect, the disclosure features a method of evaluating a drug candidate for treatment of HCV infection (e.g., chronic HCV) in a subject. The method includes providing a determination of a first level of gene expression associated with HCV infection in the subject at a first time point (e.g., wherein the first time point is prior to, or within about 1, 2, 3, 4, or 5 days of the commencement of, administration of an anti-HCV therapy (e.g., an HCV protease inhibitor, e.g., VX-950)); providing a determination of a second level of gene expression in the subject at a second time point after the first time point and preferably the second time point is after commencement of administration of anti-HCV therapy (e.g., wherein the second time point is taken at least 1, 2, 3, 4, 5, or more days after the first time point or wherein the second time point is 7, 8, 9, 10, 11, 12,

13, 14 or more days after the commencement of administration of the anti-HCV therapy); providing a comparison of the first and second levels of gene expression; and determining if the levels of gene expression are sustained (e.g., the levels differ by no more than about 60%, about 50%, about 40%, about 30%, about 20%, about 10%, about 5%, about 2%, or about 1%) between the first and second time points, thereby evaluating the drug candidate.

In some embodiments, the comparison of the first and second levels of gene expression comprises comparing the levels of one or more interferon-sensitive genes (ISG). In some embodiments, the ISG is selected from the group consisting of: IFIT1, RSAD2, IFIT2, IFI16, IFI44, IFIT2, IFIT5, PLSCR1, IFIT3, IFI35, IFITM1, IFITM3, IFI30, IFITM1, IFITM2, GIP2, OAS3, IFIT3, MX1, IFIL44L, IFI27, IFIT2A, PRSAD, or IFITA. In some preferred embodiments, first and second levels of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or all of: GIP2, OAS3, IFIT3, MX1, IFIL44L, PLSCR1, IFI27, IFIT2A, PRSAD, or IFITA are compared.

In another aspect, the disclosure features a method of evaluating a drug candidate for treatment HCV infection (e.g., chronic HCV) in a subject. The method includes providing a determination of a first level of gene expression associated with HCV infection in the subject at a first time point (e.g., wherein the first time point is prior to, or within about 1, 2, 3, 4, or 5 days of the commencement of, administration of an anti-HCV therapy (e.g., an HCV protease inhibitor, e.g., VX-950)); providing a determination of a second level of gene expression in the subject at a second time point after the first time point and preferably the second time point is after commencement of administration of anti-HCV therapy (e.g., wherein the second time point is taken at least 1, 2, 3, 4, 5, or more days after the first time point or wherein the second time point is 7, 8, 9, 10, 11, 12, 13, 14 or more days after the commencement of administration of the anti-HCV therapy); providing a comparison of the first and second levels of gene expression to a control level of gene expression; and providing a determination of whether there is a smaller difference between the second level and the control level as compared to the difference between the first level and the control level, thereby evaluating a drug candidate.

In some embodiments, the disclosure features a the gene expression associated with HCV infection is determined for a plurality of the genes listed in Table 2. In some embodiments, the plurality includes at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 96%,
5 about 97%, about 98, or about 99% of the genes listed in Table 2. In some embodiments, the plurality includes the genes listed in Table 2.

In some embodiments, the plurality includes a gene from one or more, e.g., each of the following categories (e.g., ontology categories): organismal physiological processes; immune response (e.g., IFIT2, IFIT3, IFIT4, IFI5, IFI16, IFI27, IFI30, IFI35,
10 IFI44, IFITM1, IFITM2, IFITM3, MX1); defense response (e.g., ITGB1); response to biotic stimulus (e.g., CCR1); response to stimulus (e.g., OGG1); response to stress (e.g., CEBP/B); response to pest, pathogen, or parasite (e.g., IFI27); or response to virus (e.g., IRF7, PLSCR1). In some embodiments, the plurality includes a gene from each of 2, 3, 4, 5, 6, 7, or 8 gene ontology categories described herein.

15 In another aspect, the disclosure features a method of selecting a duration of a protease inhibitor treatment (e.g., treatment with VX-950) for an subject having an HCV infection. The method includes providing an evaluation of whether the patient is an enhanced responder or a non-enhanced responder; and performing at least one of (1) if
20 the subject is an enhanced responder selecting a treatment of a first duration, and (2) if the subject is a non-enhanced responder selecting a second duration of treatment, wherein the first treatment is shorter than the second treatment.

In some embodiments, the patient is a non-enhanced responder and a treatment duration of more than 52, 48, 36, 24, 18, 12, 10, 8, 4 or 2 weeks is selected. In other
25 embodiments, the patient is an enhanced responder and a treatment duration of less than 52, 48, 36, 24, 18, 12, 10, 8, 4 or 2 weeks is selected.

In another aspect, the disclosure features a method of selecting duration of protease inhibitor treatment (e.g., VX-950 treatment) for HCV infection (e.g., chronic
30 HCV) in a subject. The method includes providing a determination of a first level of gene expression associated with HCV infection in the subject at a first time point (e.g.,

wherein the first time point is prior to, or within about 1, 2, 3, 4, or 5 days of the commencement of, administration of an anti-HCV therapy (e.g., an HCV protease inhibitor, e.g., VX-950)); providing a determination of a second level of gene expression in the subject at a second time point after the first time point and preferably the second
5 time point is after commencement of administration of anti-HCV therapy (e.g., wherein the second time point is taken at least 1, 2, 3, 4, 5, or more days after the first time point or wherein the second time point is 7, 8, 9, 10, 11, 12, 13, 14 or more days after the commencement of administration of the anti-HCV therapy); and providing a comparison of the first and second levels of gene expression and if a sustained level of gene
10 expression (e.g., the levels differ by no more than about 60%, about 50%, about 40%, about 30%, about 20%, about 10%, about 5%, about 2%, or about 1%) is present, selecting a treatment of a first duration, and if a sustained level is not present selecting a second duration of treatment, wherein the first treatment is shorter than the second treatment.

15 In some embodiments, the first duration is for less than 52, 48, 36, 24, 18, 12, 10, 8, 4 or 2 weeks.

In some embodiments, the second duration is for more than 52, 48, 36, 24, 18, 12, 10, 8, 4 or 2 weeks.

In some embodiments, the comparison of the first and second levels of gene
20 expression includes comparing the levels of one or more interferon-sensitive genes (ISG). In some embodiments, the ISG is selected from the group consisting of: IFIT1, RSAD2, IFIT2, IFI16, IFI44, IFIT2, IFIT5, PLSCR1, IFIT3, IFI35, IFITM1, IFITM3, IFI30, IFITM1, IFITM2, GIP2, OAS3, IFIT3, MX1, IFIL44L, IFI27, IFIT2A, PRSAD, or IFITA. In some preferred embodiments, first and second levels of at least 1, 2, 3, 4, 5, 6,
25 7, 8, 9, or all of: GIP2, OAS3, IFIT3, MX1, IFIL44L, PLSCR1, IFI27, IFIT2A, PRSAD, or IFITA are compared.

In one aspect, the disclosure features a method evaluating a subject, to determine, e.g., if a subject is an enhanced responder or a non-enhanced responder, to an antiviral
30 treatment, e.g., anti-HCV treatment. The method includes optionally, administering an inhibitor of a viral protease, e.g., VX-950, to the subject; providing a post-administration

value for the level of gene expression, (determined, e.g., at the RNA or protein level), for an interferon sensitive gene (ISG) in the subject, providing a comparison of the post administration value with a reference value, (by way of example, the reference value can be the level of expression of the ISG prior to administration of the antiviral treatment),
5 thereby evaluating the subject, e.g., determining if the subject is an enhanced responder or a non-enhanced responder.

In some embodiments, the method includes assigning the subject to a class, and optionally, recording the assignment, e.g., in a computer readable record.

10 In some embodiments, the evaluation includes determining if the subject is an enhanced responder. In other embodiments, the evaluation includes determining if the subject is a non-enhanced responder.

In some embodiments, the evaluation includes providing information on which to make a decision about the subject (e.g., a decision as to the duration of treatment with an anti-viral agent (e.g., VX-950), or a decision as to which treatment should be
15 administered to a subject, and so forth).

In some embodiments, the method further includes the step of selecting the subject for a preselected treatment.

In some embodiments, the method further includes the step of selecting a duration of treatment of HCV infection (e.g., chronic HCV) in a subject.

20 In some embodiments, a determination that a subject is an enhanced responder indicates that a shorter duration of treatment can/should/will be/is administered to the subject (e.g., shorter than the treatment which is recommended for a non-enhanced responder, or a duration shorter than currently used with existing anti-viral therapies, e.g., interferon and ribavarin combination therapy, e.g., 52, 48, 36, or 24 weeks), and
25 optionally, that indication is entered into a record.

In some embodiments, a determination that a subject is a non-enhanced responder indicates that a shorter duration of treatment is counter-indicated for the subject (e.g., a duration shorter than currently used with existing anti-viral therapies, e.g., interferon and ribavarin combination therapy, e.g., 52, 48, 36, or 24 weeks), and optionally, that
30 indication is entered into a record.

In some embodiments, providing a comparison of the post administration value with a reference value includes: providing a determination of a post administration level of the ISG in the subject at a first time point (e.g., wherein the first time point is 6, 7, 8, 9, 10, 11, 12, 13, 14 or more days after the commencement of administration of the anti-HCV therapy); providing a determination of a reference value of gene expression associated with HCV infection in the subject at a second time point that is prior to the first time point (e.g., wherein the second time point is prior to, or within about 1, 2, 3, 4, or 5 days of the commencement of, administration of an anti-HCV therapy (e.g., an HCV protease inhibitor, e.g., VX-950)); and providing a comparison of the post administration level and reference value of gene expression, wherein sustained levels of gene expression (e.g., the levels differ by no more than about 60%, about 50%, about 40%, about 30%, about 20%, about 10%, about 5%, about 2%, or about 1%) between the post administration level and reference value indicates that the subject is an enhanced responder.

In some embodiments, the ISG is selected from the group consisting of: IFIT1, RSAD2, IFIT2, IFI16, IFI44, IFIT2, IFIT5, PLSCR1, IFIT3, IFI35, IFITM1, IFITM3, IFI30, IFITM1, IFITM2, GIP2, OAS3, IFIT3, MX1, IFIL44L, IFI27, IFIT2A, PRSAD, or IFITA. In some preferred embodiments, first and second levels of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or all of: GIP2, OAS3, IFIT3, MX1, IFIL44L, PLSCR1, IFI27, IFIT2A, PRSAD, or IFITA are compared.

In another aspect, the disclosure features a method of predicting treatment outcome for a subject with HCV infection (e.g., chronic HCV). The method includes using a method described herein to determine if a subject is an enhanced responder (e.g., by administering a protease inhibitor, determining a post administration value of gene expression (e.g., for an ISG), and comparing a post-administration value with a reference value) wherein a determination that the subject is an enhanced responder predicts a favorable treatment outcome. In some embodiments, the subject is a human, e.g., a human diagnosed with a viral disorder (e.g., HCV). The disorder can be chronic or acute.

In some embodiments, a viral protease inhibitor is administered to the subject, e.g., the inhibitor of a viral protease (e.g., VX-950) inhibits an HCV protease, e.g.,

NS3/4A protease. In some embodiments, the inhibitor is VX-950, SCH-503034, or BILN-261 (ciluprevir).

In some embodiments, the disorder is hepatitis C virus infection (e.g., genotype 1, 2, or 3 HCV infection).

5 In some embodiments, the subject is a human, e.g., a human diagnosed with HCV genotype 1, 2, or 3, a human that has responded well (e.g., succeeded on) or poorly (e.g., failed on) to previous treatments, a human who has previously undergone a particular treatment, a human who has not yet undergone treatment for HCV infection, a human who has been diagnosed as being co-infected with another virus (e.g., hepatitis B and/or HIV).

10 In some embodiments, the method includes providing a comparison of the post-administration value with a reference value and includes determining if the post-administration value has a predetermined relationship with the reference value, e.g., determining if the post-administration value differs from the reference value by no more than 1, 5, 10, 20, 30, 40, or 50%.

15 In some embodiments, an ISG is evaluated. In some embodiments, the ISG is selected from the group consisting of: IFIT1, RSAD2, IFIT2, IFI16, IFI44, IFIT2, IFIT5, PLSCR1, IFIT3, IFI35, IFITM1, IFITM3, IFI30, IFITM1, IFITM2, GIP2, OAS3, IFIT3, MX1, IFIL44L, IFI27, IFIT2A, PRSAD, and IFITA. In some embodiments, the ISG is selected from the group consisting of: GIP2, OAS3, IFIT3, MX1, IFIL44L, PLSCR1, IFI27, IFIT2A, PRSAD, and IFITA.

20 In some embodiments, the reference value is the level of gene expression for the interferon sensitive gene (ISG) in the subject at a first time point (e.g., wherein the first time point is prior to, or within 1, 2, 3, 4, or 5 days of the commencement of, administration of an anti-HCV therapy (e.g., an HCV protease inhibitor, e.g., VX-950)). In some embodiments, the post administration value of the ISG is the level present in the subject at least 1, 2, 3, 4, 5, or more days after the first time point or 7, 8, 9, 10, 11, 12, 13, 14 or more days after the commencement of administration of the anti-HCV therapy. In some embodiments, a subsequent post administration value is determined and the subsequent determination value is the level of the ISG present in the subject 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 days after the post administration value. In some embodiments, the post

administration value is a function of the expression of a single ISG. In some embodiments, the post administration value is a function of the expression of at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, or 24 ISGs, e.g., selected from the group consisting of: IFIT1, RSAD2, IFIT2, IFI16, IFI44, IFIT2, IFIT5, PLSCR1, IFIT3, IFI35, IFITM1, IFITM3, IFI30, IFITM1, IFITM2, GIP2, OAS3, IFIT3, MX1, IFIL44L, IFI27, IFIT2A, PRSAD, and IFITA. In some embodiments, the post administration value is a function of the expression of at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 ISGs, e.g., selected from the group consisting of: GIP2, OAS3, IFIT3, MX1, IFIL44L, PLSCR1, IFI27, IFIT2A, PRSAD, and IFITA. In some embodiments, the post administration value is a function of the expression of at least 2, but no more than 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, or 24 ISGs, e.g., selected from the group consisting of: IFIT1, RSAD2, IFIT2, IFI16, IFI44, IFIT2, IFIT5, PLSCR1, IFIT3, IFI35, IFITM1, IFITM3, IFI30, IFITM1, IFITM2, GIP2, OAS3, IFIT3, MX1, IFIL44L, IFI27, IFIT2A, PRSAD, and IFITA. In some embodiments, one, two or all of: the post administration value; the reference value, if it is determined from the patient; and the subsequent post administration value, if one is determined, are determined from peripheral blood. In some embodiments, the reference value is a function of: a level determined from the patient and/or a level which is a function of the level determined from one or more other subjects (e.g., a cohort).

In another aspect, the disclosure features a method of selecting a payment class for a course of treatment with a protease inhibitor (e.g., VX-950) for a subject having an HCV infection. The method includes providing (e.g., receiving) an evaluation of whether the patient is an enhanced responder or a non-enhanced responder; and performing at least one of (1) if the subject is an enhanced responder selecting a first payment class, and (2) if the subject is a non-enhanced responder selecting a second payment class.

In some embodiments, assignment of the patient is to the first class and the assignment authorizes payment for a course of treatment for a first duration. In some embodiments, the patient is an enhanced responder and a treatment duration of less than 52, 48, 36, 24, 18, 12, 10, 8, 4 or 2 weeks is authorized.

In some embodiments, assignment of the patient is to the second class and the assignment authorizes payment for a course of treatment for a second duration. In some embodiments, the patient is a non-enhanced responder and a treatment duration of more than 52, 48, 36, 24, 18, 12, 10, 8, 4 or 2 weeks is authorized.

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In another aspect, the disclosure features a method of selecting a payment class for a course of treatment with a protease inhibitor (e.g., VX-950) for a subject having an HCV infection. The method includes providing a determination of a first level of gene expression associated with HCV infection in the subject at a first time point (e.g.,
10 wherein the first time point is prior to, or within about 1, 2, 3, 4, or 5 days of the commencement of, administration of an anti-HCV therapy (e.g., an HCV protease inhibitor, e.g., VX-950)); providing a determination of a second level of gene expression in the subject at a second time point after the first time point and preferably the second time point is after commencement of administration of anti-HCV therapy (e.g., wherein
15 the second time point is taken at least 1, 2, 3, 4, 5, or more days after the first time point or wherein the second time point is 7, 8, 9, 10, 11, 12, 13, 14 or more days after the commencement of administration of the anti-HCV therapy); and providing a comparison of the first and second levels of gene expression, and if a sustained level of gene expression (e.g., the levels differ by no more than about 60%, about 50%, about 40%,
20 about 30%, about 20%, about 10%, about 5%, about 2%, or about 1%) is present selecting a first payment class, and if a sustained level is not present selecting a second payment class.

In some embodiments, assignment of the patient is to the first class and the assignment authorizes payment for a course of treatment for a first duration. In some
25 embodiments, the patient is an enhanced responder and a treatment duration of less than 52, 48, 36, 24, 18, 12, 10, 8, 4 or 2 weeks is authorized.

In some embodiments, assignment of the patient is to the second class and the assignment authorizes payment for a course of treatment for a second duration. In some
30 embodiments, the patient is a non-enhanced responder and a treatment duration of more than 52, 48, 36, 24, 18, 12, 10, 8, 4 or 2 weeks is authorized.

In some embodiments, the expression level of one or more interferon-sensitive genes (ISG) is provided. In some embodiments, the ISG is selected from the group consisting of: IFIT1, RSAD2, IFIT2, IFI16, IFI44, IFIT2, IFIT5, PLSCR1, IFIT3, IFI35, IFITM1, IFITM3, IFI30, IFITM1, IFITM2, GIP2, OAS3, IFIT3, MX1, IFIL44L, IFI27, IFIT2A, PRSAD, or IFITA. In some embodiments, the expression level of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or all of: GIP2, OAS3, IFIT3, MX1, IFIL44L, PLSCR1, IFI27, IFIT2A, PRSAD, or IFITA is provided.

In one aspect, the disclosure features a method of providing information on which to make a decision about a subject, or making such a decision. The method includes providing (e.g., by receiving) an evaluation of a subject, wherein the evaluation was made by a method described herein, e.g., by optionally, administering an inhibitor of a viral protease, e.g., VX-950, to the subject; providing a determination of a post administration level of gene expression for an interferon sensitive gene (ISG) in the subject, thereby providing a post administration value; providing a comparison of the post administration level with a reference value, thereby, providing information on which to make a decision about a subject, or making such a decision.

In some embodiments, the method includes making the decision.

In some embodiments, the method also includes communicating the information to another party (e.g., by computer, compact disc, telephone, facsimile, email, or letter).

In some embodiments, the decision includes selecting a subject for payment, making or authorizing payment for a first course of action if the subject is an enhanced responder and a second course of action if the subject is a non-enhanced responder.

In some embodiments, the decision includes selecting a first course of action if the post administration value has a first predetermined relationship with a reference value, and selecting a second course of action if the post administration value has a second predetermined relationship with the reference value.

In some embodiments, the decision includes selecting a first course of action if the subject is an enhanced responder and a second course of action if the subject is a non-enhanced responder.

In some embodiments, the subject is an enhanced responder and the course of action is authorization of a course of therapy. In some embodiments, the course of therapy is shorter than what is provided to an otherwise similar subject who is a non-enhanced responder, e.g., the course of therapy is less than 52, 48, 36, 24, 18, 12, 10, 8, 4 or 2 weeks.

In some embodiments, the subject is an enhanced responder and the course of action is assigning the subject to a first class. In some embodiments, assignment to the first class will enable payment for a treatment provided to the subject. In some embodiments, payment is by a first party to a second party. In some embodiments, the first party is other than the patient (e.g., subject). In some embodiments, the first party is selected from a third party payor, an insurance company, employer, employer sponsored health plan, HMO, or governmental entity. In some embodiments, the second party is selected from the subject, a healthcare provider, a treating physician, an HMO, a hospital, a governmental entity, or an entity which sells or supplies the drug. In some embodiments, the first party is an insurance company and the second party is selected from the subject, a healthcare provider, a treating physician, an HMO, a hospital, a governmental entity, or an entity which sells or supplies the drug. In some embodiments, the first party is a governmental entity and the second party is selected from the subject, a healthcare provider, a treating physician, an HMO, a hospital, an insurance company, or an entity which sells or supplies the drug.

In some embodiments, the subject is a non-enhanced responder and the course of action is authorization of a course of therapy. In some embodiments, the course of therapy is longer than what is provided to an otherwise similar subject who is an enhanced responder, e.g., the course of therapy is longer than 52, 48, 36, 24, 18, 12, 10, 8, 4 or 2 weeks. In some embodiments, the subject is a non-enhanced responder and the course of action is assigning the subject to a second class. In some embodiments, assignment to the second class will enable payment for a treatment provided to the patient (e.g., subject), e.g., treatment for a period which is longer than a preselected period (e.g., longer than the period of treatment for an enhanced responder). In some embodiments, payment is by a first party to a second party. In some embodiments, the first party is other than the subject. In some embodiments, the first party is selected from a third party

payor, an insurance company, employer, employer sponsored health plan, HMO, or governmental entity. In some embodiments, the second party is selected from the subject, a healthcare provider, a treating physician, an HMO, a hospital, a governmental entity, or an entity which sells or supplies the drug. In some embodiments, the first party is an insurance company and the second party is selected from the subject, a healthcare provider, a treating physician, an HMO, a hospital, a governmental entity, or an entity which sells or supplies the drug. In some embodiments, the first party is a governmental entity and the second party is selected from the subject, a healthcare provider, a treating physician, an HMO, a hospital, an insurance company, or an entity which sells or supplies the drug.

In some embodiments, the subject is a human, e.g., a human diagnosed with a viral disorder.

In some embodiments, the inhibitor of a viral protease inhibits an HCV protease, e.g., NS3/4A protease.

In some embodiments, the disorder is chronic or acute.

In some embodiments, the disorder is hepatitis C virus infection (e.g., genotype 1, 2, or 3 HCV infection). In some embodiments, the subject is a human, e.g., a human diagnosed with HCV genotype 1, 2, or 3, a human that has responded well (e.g., succeeded on) or poorly (e.g., failed on) to previous treatments, a human who has previously undergone a particular treatment, a human who has not yet undergone treatment for HCV infection, a human who has been diagnosed as being co-infected with another virus (e.g., hepatitis B and/or HIV).

In some embodiments, comparing the post-administration level with a reference value includes determining if the post-administration level has a predetermined relationship with the reference value, e.g., determining if the post-administration value differs from the reference value by no more than 1, 5, 10, 20, 30, 40, or 50%.

In some embodiments, the inhibitor is VX-950, SCH-503034, or BILN-261 (ciluprevir).

In some embodiments, the ISG is selected from the group consisting of: IFIT1, RSAD2, IFIT2, IFI16, IFI44, IFIT2, IFIT5, PLSCR1, IFIT3, IFI35, IFITM1, IFITM3, IFI30, IFITM1, IFITM2, GIP2, OAS3, IFIT3, MX1, IFIL44L, IFI27, IFIT2A, PRSAD,

and IFITA. In some preferred embodiments, the ISG is selected from the group consisting of: GIP2, OAS3, IFIT3, MX1, IFIL44L, PLSCR1, IFI27, IFIT2A, PRSAD, and IFITA.

In some embodiments, the reference value is the level of gene expression for the interferon sensitive gene (ISG) in the subject at a first time point (e.g., wherein the first time point is prior to, or within 1, 2, 3, 4, or 5 days of the commencement of, administration of an anti-HCV therapy (e.g., an HCV protease inhibitor, e.g., VX-950)).

In some embodiments, the post administration value of the ISG is the level present in the subject at least 1, 2, 3, 4, 5, or more days after the first time point or 7, 8, 9, 10, 11, 12, 13, 14 or more days after the commencement of administration of the anti-HCV therapy.

In some embodiments, a subsequent post administration level is determined and the subsequent determination value is the level of the ISG present in the subject 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 days after the post administration value.

In some embodiments, the post administration value is a function of the expression of a single ISG. In some embodiments, the post administration value is a function of the expression of at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, or 24 ISGs, e.g., selected from the group consisting of: IFIT1, RSAD2, IFIT2, IFI16, IFI44, IFIT2, IFIT5, PLSCR1, IFIT3, IFI35, IFITM1, IFITM3, IFI30, IFITM1, IFITM2, GIP2, OAS3, IFIT3, MX1, IFIL44L, IFI27, IFIT2A, PRSAD, and IFITA. In some embodiments, the post administration value is a function of the expression of at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 ISGs, e.g., selected from the group consisting of: GIP2, OAS3, IFIT3, MX1, IFIL44L, PLSCR1, IFI27, IFIT2A, PRSAD, and IFITA. In some embodiments, the post administration value is a function of the expression of at least 2, but no more than 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, or 25 ISGs, e.g., selected from the group consisting of: IFIT1, RSAD2, IFIT2, IFI16, IFI44, IFIT2, IFIT5, PLSCR1, IFIT3, IFI35, IFITM1, IFITM3, IFI30, IFITM1, IFITM2, GIP2, OAS3, IFIT3, MX1, IFIL44L, IFI27, IFIT2A, PRSAD, and IFITA. In some embodiments, the post administration value is a function of the expression of at least 2 ISGs wherein the value is the intrinsic expression value associated with each ISG.

In some embodiments, one, two or all of: the post administration value; the reference value, if it is determined from the patient; and the subsequent post administration value, if one is determined, are determined from peripheral blood.

In some embodiments, the reference value is a function of: a level determined
5 from the patient; and/or a level which is a function of the level determined from one or more other subjects (e.g., a cohort).

In another aspect, the disclosure features a method of selecting a payment class for a course of treatment with a protease inhibitor for a subject having an HCV infection.
10 The method includes identifying the subject as an enhanced responder, and approving, making, authorizing, receiving, transmitting or otherwise allowing payment of a selected course of treatment, e.g., a shorter course of treatment (e.g., less than 52, 48, 36, 24, 18, 12, 10, 8, 4 or 2 weeks) than if the subject has been identified as a non-enhanced responder.

In another aspect, the disclosure features a method of selecting a payment class for a course of treatment with a protease inhibitor for a subject having an HCV infection. The method includes identifying the subject as a non-enhanced responder, and approving, making, authorizing, receiving, transmitting or otherwise allowing payment of a selected
20 course of treatment, e.g., a longer course of treatment (e.g., more than 52, 48, 36, 24, 18, 12, 10, 8, 4 or 2 weeks) than if the subject had been identified as an enhanced responder.

In one aspect, the disclosure features a method of making a data record. The method includes entering the result of a method described herein into a record, e.g., a
25 computer readable record. In some embodiments, the record is available on the world wide web. In some embodiments, the record is evaluated by a third party payor, an insurance company, employer, employer sponsored health plan, HMO, or governmental entity, or a healthcare provider, a treating physician, an HMO, a hospital, a governmental entity, or an entity which sells or supplies the drug, or is otherwise relied on in a method
30 described herein.

In another aspect, the disclosure features a data record (e.g., computer readable record), wherein the record includes results from a method described herein. In some embodiments, the record is available on the world wide web. In some embodiments, the record is evaluated and/or transmitted to a third party payor, an insurance company,
5 employer, employer sponsored health plan, HMO, or governmental entity, or a healthcare provider, a treating physician, an HMO, a hospital, a governmental entity, or an entity which sells or supplies the drug.

In one aspect, the disclosure features a method of providing data. The method
10 includes providing data described herein, e.g., generated by a method described herein, to provide a record, e.g., a record described herein, for determining if a payment will be provided. In some embodiments, the data is provided by computer, compact disc, telephone, facsimile, email, or letter. In some embodiments, the data is provided by a first party to a second party. In some embodiments, the first party is selected from the
15 subject, a healthcare provider, a treating physician, an HMO, a hospital, a governmental entity, or an entity which sells or supplies the drug. In some embodiments, the second party is a third party payor, an insurance company, employer, employer sponsored health plan, HMO, or governmental entity. In some embodiments, the first party is selected from the subject, a healthcare provider, a treating physician, an HMO, a hospital, an
20 insurance company, or an entity which sells or supplies the drug and the second party is a governmental entity. In some embodiments, the first party is selected from the subject, a healthcare provider, a treating physician, an HMO, a hospital, an insurance company, or an entity which sells or supplies the drug and the second party is an insurance company.

25 In another aspect, the disclosure features a signature set of probes having a probe for each of the genes in a signature set described herein, e.g., each of a plurality of genes each of which is differentially expressed as between virally infected individuals and non-infected individuals, and contains a sufficient number of differentially expressed genes such that if each of the genes in the signature set is differentially expressed as compared
30 to a non infected reference, it is predictive of infection with no more than about 15, about 10, about 5, about 2.5, or about 1% false positives.

In some embodiments, the signature set of probes includes probes for a plurality of genes listed in Table 2. In some embodiments, the signature set of probes includes probes for at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 96%, about 97%, about 98, or about 99% of the genes listed in Table 2. In some embodiments, the signature set of probes includes probes for the genes listed in Table 2.

In some embodiments, the signature set of probes includes a probe for a gene from one or more, e.g., each of the following categories (e.g., ontology categories): organismal physiological processes; immune response (e.g., IFIT2, IFIT3, IFIT4, IFI5, IFI16, IFI27, IFI30, IFI35, IFI44, IFITM1, IFITM2, IFITM3, MX1); defense response (e.g., ITGB1); response to biotic stimulus (e.g., CCR1); response to stimulus (e.g., OGG1); response to stress (e.g., CEBP/B); response to pest, pathogen, or parasite (e.g., IFI27); or response to virus (e.g., IRF7, PLSCR1). In some embodiments, the signature set of probes includes probes for a gene from each of 2, 3, 4, 5, 6, 7, or 8 of the gene ontology categories.

In some embodiments, the signature set of probes includes probes for one or more interferon-sensitive genes (ISG). In some embodiments, the ISG is selected from the group consisting of: IFIT1, RSAD2, IFIT2, IFI16, IFI44, IFIT2, IFIT5, PLSCR1, IFIT3, IFI35, IFITM1, IFITM3, IFI30, IFITM1, IFITM2, GIP2, OAS3, IFIT3, MX1, IFIL44L, IFI27, IFIT2A, PRSAD, or IFITA. In some preferred embodiments, the signature set of probes includes probes for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or all of: GIP2, OAS3, IFIT3, MX1, IFIL44L, PLSCR1, IFI27, IFIT2A, PRSAD, or IFITA.

In some embodiments, the signature set of probes includes probes for at least 20, 40, 60, 80, 100, 150, or 200 genes.

In some embodiments, the signature set of probes includes probes for no more than 20, 40, 60, 80, 100, 150, or 200 genes.

In another aspect, the disclosure features a record (e.g., computer readable record) which includes a list and value of expression for each gene represented in the signature set. In some embodiments, the record includes more than one value for each gene, wherein a first value (e.g., pre treatment, e.g., wherein the first value is obtained at a first

time point that is prior to, or within 1, 2, 3, 4, or 5 days of the commencement of, administration of an anti-HCV therapy) and a second value (e.g., wherein the second value is obtained post treatment administration, e.g., at least 1, 2, 3, 4, 5, or more days after the first time point or at 7, 8, 9, 10, 11, 12, 13, 14 or more days after the commencement of administration of the anti-HCV therapy) are provided for each gene.

In one aspect, the disclosure features a method of transmitting a record described herein. The method includes a first party transmitting the record to a second party, e.g., by computer, compact disc, telephone, facsimile, email, or letter. In some embodiments, the second party is selected from the subject, a healthcare provider, a treating physician, an HMO, a hospital, a governmental entity, or an entity which sells or supplies the drug. In some embodiments, the first party is an insurance company or government entity and the second party is selected from the subject, a healthcare provider, a treating physician, an HMO, a hospital, a governmental entity, or an entity which sells or supplies the drug. In some embodiments, the first party is a governmental entity or insurance company and the second party is selected from the subject, a healthcare provider, a treating physician, an HMO, a hospital, an insurance company, or an entity which sells or supplies the drug.

In another aspect, the disclosure features an array including a plurality of spatially distinguishable regions, each region having a probe specific for a gene from a signature set of genes described herein, and the array having at least one of the following properties:

if probe specific spatially distinguishable regions for genes other than those in the signature set are present, spatially distinguishable regions for signature set specific probes account for at least 10, 20, 30, 50, 75, 80, 90, 99 % of the total probe specific spatially distinguishable regions of the array;

no more than 10, 100, 500, 1,000, 5,000, or 10,000 probe specific spatially distinguishable regions for genes other than those in the signature set are present on the array;

the array is in contact with nucleic acids derived from a subject who has been administered a protease inhibitor, e.g., VX-950, SCH-503034, or BILN-261 (ciluprevir); or

the array is in contact with nucleic acids derived from a subject who has HCV.

5 In some embodiments, the array includes a duplicate, or triplicate of 1, 5, 10, 20 or all of the regions having a probe specific for a gene from a signature set of genes.

In another aspect, the disclosure features a method of providing data. The method includes providing hybridization data from contacting an array including a plurality of spatially distinguishable regions described herein with a nucleic acid sample derived from a subject (e.g., a subject described herein), and providing a record of such data.

In some embodiments, the subject has an HCV infection.

In some embodiments, the record includes data from hybridizing nucleic acid from the subject prior to administration of a protease inhibitor, e.g., VX-950, to the subject.

In some embodiments, the record includes data from hybridizing nucleic acid from the subject after administration of a protease inhibitor, e.g., VX-950 to the subject.

In some embodiments, the record includes a value which is a function of comparing pre and post administration data.

In another aspect, an evaluation of the ratio of gene expression of ISGs prior to dosing (e.g., with VX-950) in enhanced responders as compared to non-enhanced responders demonstrates that for many ISGs, the pre-dose expression levels are elevated as compared to the levels in non-enhanced responders (see, e.g., Table 5). Thus, the levels of an ISG, e.g., an ISG shown in Table 5 (e.g., IFIT4, IFI44L, RSAD2, IFIT2, IFIT3, IFI16, IFI44, IFIT5, PLSCR1), can be determined for a subject to generate a value that is a function of the ISG level in the subject. This value for the subject can then be compared to a reference value. For example, if the subject's value is compared to a value from an enhanced responder (or cohort of enhanced responders) and the subject's value is similar to this reference value, this can be used to predict that the subject will also be an enhanced responder. If the subject value is compared to a value from a non-enhanced

responder (or a cohort of non-enhanced responders) and the subject's value is similar to this reference, this can be used to predict that the subject may not be an enhanced responder. The results of a classification as an enhanced or non-enhanced responder are described herein.

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The term "gene expression" as used herein refers to an indicium of levels of gene expression, such as RNA (e.g., mRNA) levels, cDNA levels, and protein levels. The term "gene transcript" as used herein refers to either the full length transcript for a particular gene or to a portion of that transcript (e.g., oligonucleotide, e.g., probe) that allows
10 identification of that portion as corresponding (e.g., specifically) to a particular full length transcript, particular isoform, splice variant or other variant, or polymorphism thereof. Thus, the term "gene transcript" also includes biomarkers of a particular gene transcript, e.g., a biomarker that can be present on a two dimensional array, e.g., gene chip.

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A "signature set of genes" as used herein refers to a plurality of gene transcripts, each of which is differentially expressed as between virally (e.g., HCV) infected subjects and non infected subjects and contains a sufficient number of differentially expressed genes such that if each of the genes in the signature set is differentially expressed as compared to a non infected reference (e.g., non infected individual or cohort of non
20 infected individuals), it is predictive of infection in a test subject for whom the presence or absence of infection is being determined. The signature set can be predictive of the presence of infection (e.g., an HCV infection) with no more than about 15%, about 10%, about 5%, about 2.5%, or about 1% false positives. The signature set can have a preset limit for a false discovery rate (e.g., less than about 10%, about 5%, about 2.5%, or about
25 1%).

As described herein, gene expression can be measured, e.g., by assaying RNA or cDNA levels, or levels of a polypeptide encoded by a given gene transcript.

As used herein, an "interferon-sensitive gene" (ISG) refers to a gene whose expression is affected by interferon signaling, e.g., interferon signaling can cause
30 increased or decreased expression of the ISG. For example, an ISG can have an interferon-stimulated response element (ISRE) in its 5' upstream region.

As used herein, the term “value” (e.g., determined value, post administration value, reference value) refers to a value that is a function of the level of expression of a gene transcript. For example, a value for a gene can be based on the expression level (e.g., RNA or protein levels) of the gene. The value need not equal a measured
5 expression level. For example, arriving at a value may involve subtracting out background levels, amplifying the level by some determined factor, determining an averaging level from a cohort of subjects, and/or otherwise adjusting the value.

The term “normalization of the signature set” indicates that the signature of a subject varies by less than about 50%, about 40%, about 30%, about 20%, about 10%,
10 about 5%, about 4%, about 3%, about 2%, or about 1% from the signature of a reference (e.g., non-HCV infected subject or cohort of non-HCV infected subjects).

An “enhanced responder”, as used herein, refers to a subject that responds significantly more quickly as compared to a “non-enhanced responder” to anti-viral treatment (e.g., anti-viral protease treatment, e.g., VX-950), in the sense that viral titers
15 decrease significantly more quickly in the enhanced responder. In one embodiment, an enhanced responder will have no more than about 35%, about 50%, about 60%, or about 75% of the viral titer of an otherwise similar non-enhanced responder, where titer can be measured as international units (I.U.) of viral (e.g., HCV) RNA/ml of blood at 14 days after the beginning of treatment. For example, an enhanced responder can have less than
20 or equal to 35 I.U. of HCV RNA/ml at 14 days after the commencement of treatment, while a “non-enhanced responder”, can have greater than or equal to 100 I.U. of HCV RNA/ml at 14 days after the commencement of treatment (e.g., where titers are measured by the COBAS AmpliPrep/COBAS TAQMAN™ HCV Test (Roche Molecular
Diagnostics)). Alternatively, an enhanced responder can also be identified by ISG
25 expression. In some embodiments, e.g., in which first and second levels of an ISG are compared, sustained levels of the gene transcript (e.g., the levels differ by no more than about 60%, about 50%, about 40%, about 30%, about 20%, about 10%, about 5%, about 2%, or about 1%) between the first and second time points, e.g., a first time point that is
prior to, or within 1, 2, 3, 4, or 5 days of the commencement of, administration of an anti-
30 HCV therapy and the second time point is after commencement of administration of anti-HCV therapy, e.g., wherein the second time point is taken at least 1, 2, 3, 4, 5, or more

days after the first time point or wherein the second time point is 7, 8, 9, 10, 11, 12, 13, 14 or more days after the commencement of administration of the anti-HCV therapy, indicate that the subject is an enhanced responder and, e.g., the duration of treatment for the enhanced responder can be shorter than for a non-enhanced responder.

5 A signature set described herein can be evaluated for specific groups of subjects, e.g., males, females, HCV genotype 1, 2, or 3, particular age groups, races, subjects that have responded well or poorly to previous treatments (e.g., the same or different treatment), subjects who have previously undergone a particular treatment (e.g., the same or different treatment), subjects who have not yet undergone any treatment for HCV
10 infection, subjects who have been diagnosed as being co-infected with another virus (e.g., hepatitis B and/or HIV) and who may or may not have undergone treatment for the other virus, subjects with alcoholic liver disease, etc.

All cited patents, patent applications, and references are hereby incorporated by
15 reference in their entireties. In the case of conflict, the present application controls.

The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

20 DESCRIPTION OF DRAWINGS

FIG. 1 is a line graph demonstrating median HCV RNA levels (y axis) over time (x axis) in HCV infected patients after treatment with VX-950 or a placebo control.

FIG. 2 is a graph depicting the correlation of patients receiving VX-950 over time with healthy subject gene expression levels.

25 FIGS. 3A, 3B, and 3C demonstrate the correlation between sustained levels of IFN-sensitive genes (ISG) and a reduction in plasma HCV RNA levels. FIG. 3A shows mean ratios of IFN-induced gene expression levels (day 14 vs. pre-dose). There is a statistically significant difference in the sustained expression levels of the ISGs. FIG. 3B shows sustained levels of the ISGs in five enhanced responders (left-most bars) who were
30 HCV RNA undetectable at day 14. FIG. 3C shows quantitative real-time PCR

confirmation of Affymetrix genechip results. Gene expression modulation of specific ISGs for each of the three groups in FIG. 3B are shown (top left panel shows the results for the enhanced responders while the top right and bottom panels show the results for the non-enhanced responders).

DETAILED DESCRIPTION

The inventors have identified a signature set associated with chronic HCV infection. One or more of the genes of the signature can be used, for example, to diagnose HCV infection, predict the treatment outcome of a subject with HCV, select a treatment regimen, select dosages of a given treatment, evaluate a drug candidate, and/or select the duration of a treatment regimen. The pattern or levels of expression of a plurality of gene transcripts of the signature can correlate with a given treatment regimen or outcome prediction.

Further, the inventors have identified interferon-sensitive genes (ISGs) whose expression levels can change upon HCV infection. For subjects who achieved undetectable plasma HCV status (e.g., enhanced responders), sustained expression of the ISGs was observed, e.g., in peripheral blood (e.g., mononuclear cells). Thus, baseline and/or sustained expression levels of the ISGs can be used to predict treatment outcomes.

Hepatitis C Virus Infection

Hepatitis C: Hepatitis C is a viral infection of the liver and is a major cause of acute hepatitis and chronic liver disease, including cirrhosis and liver cancer. HCV is one of the viruses (A, B, C, D, and E), which together account for the vast majority of cases of viral hepatitis. HCV is an enveloped RNA virus in the *flaviviridae* family which appears to have a narrow host range. Humans and chimpanzees are the only known species susceptible to infection, with both species developing similar disease. An important feature of the virus is the relative mutability of its genome, which may be related to its high propensity (80%) of inducing chronic infection.

The incubation period of HCV infection before the onset of clinical symptoms ranges from 15 to 150 days. In acute infections, the most common symptoms are fatigue and jaundice; however, the majority of cases (between 60% and 70%), even those that

develop chronic infection, are asymptomatic. Other symptoms of HCV infection include: dark urine, abdominal pain, loss of appetite, and nausea.

About 80% of newly infected patients progress to develop chronic infection. Cirrhosis develops in about 10% to 20% of persons with chronic infection, and liver cancer develops in 1% to 5% of persons with chronic infection over a period of 20 to 30 years. Most patients suffering from liver cancer who do not have hepatitis B virus infection have evidence of HCV infection. Hepatitis C also exacerbates the severity of underlying liver disease when it coexists with other hepatic conditions. In particular, liver disease progresses more rapidly among persons with alcoholic liver disease and HCV infection.

B cells, monocytes, and dendritic cells take up HCV particles, and degradation of the particles releases viral proteins and dsRNA that activate gene expression in peripheral blood cells. Clearance of plasma HCV RNA and elimination of virus particles can result in normalization of the signature set. Persistence of differential expression, and lack of normalization, of the 258-gene signature set correlates with the presence of HCV RNA, e.g., 2-3 logs of plasma HCV RNA.

Diagnosis: Diagnostic tests for HCV are used to prevent infection through screening of donor blood and plasma, to establish the clinical diagnosis and to make better decisions regarding medical management of a patient. Diagnostic tests commercially available today are based on enzyme immunosorbant assays (EIA) for the detection of HCV specific antibodies. EIAs can detect more than 95% of chronically infected patients but can detect only 50% to 70% of acute infections.

A recombinant immunoblot assay (RIBA) that identifies antibodies which react with individual HCV antigens can be used as a supplemental test for confirmation of a positive EIA result.

Testing for HCV RNA by amplification methods (e.g., polymerase chain reaction (PCR) or branched DNA assay) can also be utilized for confirmation of serological results as well as for assessing the effectiveness of antiviral therapy. A positive result indicates the presence of active infection and a potential for spread of the infection and or/the development of chronic liver disease.

Genotypes: There are six known genotypes and more than 50 subtypes of HCV, and genotype information is helpful in defining the epidemiology of hepatitis C.

Knowing the genotype or serotype (genotype-specific antibodies) of HCV is helpful in making recommendations and counseling regarding therapy. Patients with genotypes 2

5 and 3 are almost three times more likely than patients with genotype 1 to respond to therapy with alpha interferon or the combination of alpha interferon and ribavirin.

Furthermore, when using combination therapy, the recommended duration of treatment depends on the genotype. For patients with genotypes 2 and 3, a 24-week course of combination treatment can be adequate, whereas for patients with genotype 1, a 48-week
10 course is often recommended. For these reasons, testing for HCV genotype is often clinically helpful.

Interferon-Sensitive Genes (ISG)

Interferons (IFN) are classified into two distinct types, designated as type I (IFN-alpha, IFN-beta, IFN-omega, IFN-tau) and type II (IFN-gamma) according to their
15 cellular origin, inducing agents and antigenic and functional properties. Interferons affect the expression of a number of genes following interaction with specific high-affinity plasma membrane receptors. The products of these genes either singly or coordinately mediate the antiviral, growth inhibitory or immunoregulatory activities attributed to IFN.

A feature common to most of not all IFN-sensitive genes is the presence of a DNA
20 element which constitutes an IFN-responsive enhancer, usually present in the 5' upstream region of the genes. This element, termed interferon-stimulated response element (ISRE) binds a nuclear factor(s) translocated from the cytoplasm to the nucleus following IFN-receptor-triggered signal transduction. The binding of these factors to the ISRE

represents the initiating event in stimulating RNA-polymerase-II- mediated transcription
25 from IFN-sensitive genes. Depending on the nature of the cells responding to IFN and the genes involved, induced transcription may be prolonged or rapidly terminated. The rapid termination of transcription is dependent in some cases on IFN-induced protein synthesis and also involves factor binding to the ISRE. The ISGs are involved in mediating the antiviral effect of IFN. ISGs include genes that pertain to the functioning
30 of immune cells, including genes involved in antigen processing and presentation, T-cell

activation, lymphocyte trafficking, and effector functions. The ISGs can enhance immunity against viruses, e.g., HCV. Examples of ISGs are listed in Table 5.

Sustained expression of ISGs was seen in subjects who cleared plasma HCV RNA. This can reflect restored intrinsic antiviral defenses and secretion of interferons, and may be a sign of re-emergence of an effective immune response that is essential to eliminate residual HCV infected hepatocytes. Expression of ISGs and other genes associated with acquired immunity may be monitored to establish potential correlations with, and to make predictions of, treatment outcomes. Further, gene or protein therapy with an ISG (e.g., an ISG listed in Table 5), can be used alone or as part of an anti-viral (e.g., anti-HCV) therapy, e.g., gene or protein therapy with an ISG can be used in combination with an anti-viral agent, e.g., an HCV protease inhibitor, e.g., VX-950, SCH-503034, or BILN-261 (ciluprevir).

Treatment of HCV

Antiviral drugs such as interferon taken alone or in combination with ribavirin, can be used for the treatment of persons with chronic hepatitis C. Treatment with interferon (or pegylated interferon) (e.g., interferon-alpha) alone is effective in about 10% to 20% of patients. Interferon (or pegylated interferon) combined with ribavirin is effective in about 30% to 50% of patients. Additional treatments include VX-950, either alone or in combination with interferon (or pegylated interferon) and/or ribavirin, or another anti-viral or immunomodulatory agent.

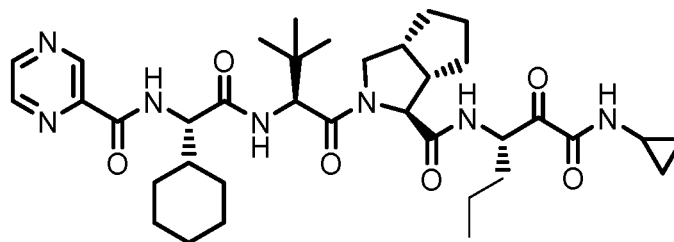
There is no vaccine against HCV. Research is in progress but the high mutability of the HCV genome complicates vaccine development.

The inventions described herein can be used as part of the evaluation of a subject with HCV and/or in the selection of a suitable treatment regimen, e.g., VX-950 alone or in combination with another agent, or another therapy (e.g., another monotherapy or combination therapy) described herein. For example, the methods and reagents described herein can be used to select a treatment regimen for a subject, e.g., a subject that has been identified as being an enhanced responder or non-enhanced responder.

VX-950

VX-950 is a competitive, reversible peptidomimetic HCV NS3/4A protease inhibitor with a steady state binding constant (k_i^*) of 3nM (and with a K_i of 8 nM) and is described in International Application WO 02/018369.

5 The structure of VX-950 is:



VX-950

VX-950 is highly insoluble in water. VX-950 may be prepared by methods known to those skilled in the art (see, e.g., International Applications WO 02/18369 and WO 2005/123076; U.S. App. No. 11/147,524 (filed June 8, 2005)). VX-950 can be formulated into tablets, as described in U.S. App. Nos. 60/764,654 (filed February 2, 2006), 60/784,427 (filed March 20, 2006), 60/784,428 (filed March 20, 2006), 60/784,275 (filed March 20, 2006), 11/687,716 (filed March 10, 2007), 11/687,779 (filed March 19, 2007), PCT App. No. PCT/US2007/061456 (filed February 1, 2007).

15 Inhibition of NS3/4A by VX-950 can restore IFN signaling and block viral replication in hepatocytes and cleavage of TRIF/CARDIF, thereby restoring IRF3 and RIG-1 signaling and transcription of ISGs that can activate intrinsic anti-viral defenses, including production of IFN β , in hepatocytes.

Treatment with VX-950

20 VX-950 Monotherapy: Dosage levels of from about 0.01 to about 100 mg/kg body weight per day, preferably from about 10 to about 100 mg/kg body weight per day of VX-950 are useful for the prevention and treatment of HCV mediated disease. In some embodiments, dosage levels from about 0.4 to about 10 g/day, for example from about 1 to about 4 g/day, preferably from about 2 to about 3.5 g/day, per person (based on the average size of a person calculated at about 70 kg) are included. Typically, the pharmaceutical compositions of, and according to, this invention will be administered

25

from about 1 to about 5 times per day, preferably from about 1 to about 3 times per day, or alternatively, as a continuous infusion. In some embodiments, VX-950 is administered using a controlled release formulation. In some embodiments, this can help to provide relatively stable blood levels of VX-950.

5 In some embodiments, amorphous VX-950 is administered. The dose of amorphous VX-950 can be a standard dose, e.g., about 1 g to about 5 g a day, more preferably about 2 g to about 4 g a day, more preferably about 2 g to about 3 g a day, e.g., about 2.25 g or about 2.5 g a day. For example, a dose of about 450 mg, 750 mg, or 1250 mg can be administered to a subject three times a day. A dose of 1250 mg can be given
10 twice daily. For example, a dose of about 2.25 g/day of amorphous VX-950 can be administered to a patient, e.g., about 750 mg administered three times a day. Such a dose can be administered, e.g., as three 250 mg doses three times a day or as two 375 mg doses three times a day. In some embodiments, the 250 mg dose is in an about 700 mg tablet. In some embodiments, the 375 mg dose is in an about 800 mg tablet. As another
15 example, a dose of about 2.5 g/day of amorphous VX-950 can be administered to a patient, e.g., about 1250 mg administered two times a day. As another example, about 1 g to about 2 g of amorphous VX-950 a day can be administered to a patient, e.g., about 1.35 g of amorphous VX-950 can be administered to a patient, e.g., about 450 mg administered three times a day. The dose of amorphous VX-950 can be administered
20 e.g., as a spray dried dispersion or as a tablet (e.g., a tablet that comprises VX-950, e.g., in a spray dried dispersion).

In some embodiments, the solid (e.g., spray dried) dispersions of VX-950 described herein contain at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about
25 85% or greater of VX-950 (e.g., amorphous VX-950). Because these dispersions can include greater amounts of VX-950 for a given amount of a dispersion (e.g., a greater percent by weight of VX-950), for the same amount by weight of solid dispersion, a greater amount of VX-950 can be incorporated into a pharmaceutical composition, thereby increasing the load of the active ingredient in that composition. As a result, a
30 subject receiving VX-950 can take fewer doses of VX-950 and yet intake the same amount of drug. For example, to receive a dose of 750 mg of VX-950, a subject can take

two 375 mg doses of VX-950 containing a solid dispersion described herein instead of three 250 mg doses. This can be an improvement or a preferred dose for some patients. As another example, the increased load of amorphous VX-950 in a solid dispersion can allow administration of a larger dose of VX-950 to a subject in a fixed total dose of a pharmaceutical composition (e.g., a tablet of a standard size may contain a larger percentage (and thereby dose) of amorphous VX-950). Conversely, the increased load of amorphous VX-950 can allow a fixed dose amount of amorphous to be administered to a subject in a small total dose of a pharmaceutical composition (e.g., a standard dose of amorphous VX-950 can be administered in a smaller tablet).

In some embodiments, the amorphous VX-950 is not 100% potent or pure (e.g., the potency or purity is at least about 90%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% potent), in which case the doses described above refer to the amount of potent or pure VX-950 administered to a patient rather than the total amount of VX-950. These doses can be administered to a patient as a monotherapy and/or as part of a combination therapy, e.g., as described further below.

Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the subject treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Preferably, such preparations contain from about 20% to about 80%, from about 25% to about 70%, from about 30% to about 60% active compound.

When the compositions or methods of this disclosure involve a combination of VX-950 and one or more additional therapeutic or prophylactic agents, both the compound and the additional agent should be present at dosage levels of between about 10 to 100%, and more preferably between about 10 to 80% of the dosage normally administered in a monotherapy regimen.

Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this disclosure may be administered, if necessary.

Subsequently, the dosage or frequency of administration, or both, may be reduced, e.g., to about 1/2 or 1/4 or less of the dosage or frequency of administration, as a function of the

symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level, treatment should cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

5 It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, influence of any previous therapies undergone by the subject, and the judgment of the treating physician and the severity of
10 the particular disease being treated. The amount of active ingredients will also depend upon the particular described compound and the presence or absence and the nature of the additional anti-viral agent in the composition.

Combination Therapy

15 More than one therapeutic agent can be used to treat HCV.

 In some embodiments, two or more agents to treat HCV can be started at the same time or within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or more days of each other, or optionally, can be administered sequentially. In combination therapy, the course of the first and second agents can be the same, can overlap but be different, or can be
20 sequential, e.g., the course of the first agent is given and then a course of the second agent is given. In a preferred embodiment, therapeutic levels of both agents are present for at least a portion of the therapy.

 In some embodiments, a protease inhibitor, e.g., VX-950, is administered to a subject and ISG (e.g., one or more of the ISGs described herein) expression is measured.
25 In some embodiments, ISG expression is measured prior to, or within about 1, 2, 3, 4, or 5, days of the commencement of, administration of the protease inhibitor (first time point) and/or at least 1, 2, 3, 4, 5, or more days after the first time point or at least 7, 8, 9, 10, 11, 12, 13, 14 or more days after the commencement of the protease inhibitor, and optionally at another time point. If ISG expression is measured at more than one time
30 point, the levels of ISG expression can be compared. For example, if ISG levels are sustained at the two time points, the subject can be classified as an enhanced responder; if

ISG levels are not sustained, the subject can be classified as a non-enhanced responder, as described herein. The classification of the subject can be used to decide a treatment regimen, as described herein. After the ISG level is measured at one or more time points, a second therapy (e.g., while continuing with the first treatment with the protease inhibitor) can optionally be started, e.g., interferon, ribavarin, a second protease inhibitor, or other therapy described herein, can be administered to the subject. The second therapy can be initiated within about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or more days of the initiation of the first therapy. The second therapy can be maintained for the duration of the treatment of the first therapy, or for a longer or shorter period than the period used for the first therapy. For example, the second therapy can be administered at a dose and for a duration previously known for that therapy (e.g., peg-interferon or ribavarin).

Examples of agents that can be used to treat HCV infection, alone or in combination therapies (e.g., with another agent described therein or with VX-950), are described in International Publication WO 02/18369. The combinations specifically recited therein can be combined with methods described herein. The methods and reagents described herein can be used to select a treatment regimen (e.g., a combination therapy) for a subject, e.g., a subject that has been identified as being an enhanced responder or non-enhanced responder.

VX-950 Combination Therapy: VX-950 can optionally be administered with another component comprising an additional agent, e.g., selected from an immunomodulatory agent; an antiviral agent; an inhibitor of HCV protease; an inhibitor of another target in the HCV life cycle; an inhibitor of internal ribosome entry; a broad-spectrum viral inhibitor; a cytochrome P-450 inhibitor(s); or combinations thereof.

Accordingly, in another embodiment, this invention provides a method comprising administering any form of VX-950, any solid dispersion, or any composition according to this invention, a CYP inhibitor, and another anti-viral agent, preferably an anti-HCV agent. Such anti-viral agents include, but are not limited to, immunomodulatory agents, such as α -, β -, and γ -interferons, pegylated derivatized interferon- α compounds, and thymosin; other anti-viral agents, such as ribavirin, amantadine, and telbivudine; other inhibitors of hepatitis C proteases (NS2-NS3

inhibitors and NS3/NS4A inhibitors); inhibitors of other targets in the HCV life cycle, including helicase, polymerase, and metalloprotease inhibitors; inhibitors of internal ribosome entry; broad-spectrum viral inhibitors, such as IMPDH inhibitors (e.g., compounds of U.S. Pat. Nos. 5,807,876, 6,498,178, 6,344,465, 6,054,472; International Applications WO 97/40028, WO 98/40381, WO 00/56331, and mycophenolic acid and derivatives thereof, and including, but not limited to VX-497, VX-148, and/or VX-944); or combinations of any of the above.

A preferred combination therapy comprises a formulation of amorphous VX-950 described herein and interferon- α , e.g., pegylated derivatized interferon- α (e.g., pegylated interferon-alpha-2a; e.g., PEGASY[®], e.g., at its standard dose). For example, a dose (e.g., as described above) of amorphous VX-950, e.g., about 2 g to about 3 g (e.g., 2.5 g, 2.25 g (e.g., 750 mg three times a day)), e.g., in the form of a tablet described herein can be administered three times a day and pegylated interferon-alpha-2a can be administered at a standard dose, e.g., 180 μ g once weekly by subcutaneous administration, e.g., for 48 or 52 weeks. As another example, VX-950 can be administered with both pegylated interferon-alpha-2 and ribavirin. For example, about 2 g to about 3 g (e.g., about 2.5 g, about 2.25 g (e.g., 750 mg three times a day)) of amorphous VX-950 in the form of a tablet described herein, can be administered three times a day in combination with 180 μ g of pegylated interferon-alpha-2a (e.g., PEGASY[®]) once a week and ribavirin (e.g., COPEGUS[®]; (1-beta-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide, available from ICN Pharmaceuticals, Inc., Costa Mesa, CA; described in the Merck Index, entry 8365, Twelfth Edition) at 1000-1200 mg/day, e.g., for 48 or 52 weeks, for genotype 1 patients, or in combination with 180 μ g of pegylated interferon-alpha-2a once a week plus ribavirin at 800 mg/day for patients with genotype 2 or 3 hepatitis C.

Other agents that can be used in combination with VX-950 include those described in various published U.S. Patent Applications. These publications provide additional teachings of compounds and methods that could be used in combination with VX-950 in the methods of this invention, particularly for the treatment of hepatitis. It is contemplated that any such methods and compositions may be used in combination with the methods and compositions of the present invention. For brevity, the disclosure the

disclosures from those publications is referred to by reference to the publication number. Exemplary such publications include U.S. Pub. Nos. 20040058982; 20050192212; 20050080005; 20050062522; 20050020503; 20040229818; 20040229817; 20040224900; 20040186125; 20040171626; 20040110747; 20040072788; 20040067901; 20030191067; 20030187018; 20030186895; 20030181363; 20020147160; 20040082574; 20050192212; 20050187192; 20050187165; 20050049220; and US20050222236.

Additional examples of agents include, but are not limited to, ALBUFERONTM (albumin-Interferon alpha) available from Human Genome Sciences; PEG-INTRON[®] (peginterferon alfa-2b, available from Schering Corporation, Kenilworth, NJ); INTRON-A[®], (VIRAFERON[®], interferon alfa-2b available from Schering Corporation, Kenilworth, NJ); REBETROL[®] (Schering Corporation, Kenilworth, NJ); COPEGUS[®] (Hoffmann-La Roche, Nutley, NJ); PEGASYS[®] (peginterferon alfa-2a available Hoffmann-La Roche, Nutley, NJ); ROFERON[®] (recombinant interferon alfa-2a available from Hoffmann-La Roche, Nutley, NJ); BEREFOR[®] (interferon alfa 2 available from Boehringer Ingelheim Pharmaceutical, Inc., Ridgefield, CT); SUMIFERON[®] (a purified blend of natural alpha interferons such as Sumiferon available from Sumitomo, Japan); WELLFERON[®] (interferon alpha n1 available from Glaxo Wellcome Ltd., Great Britain); ALFERON[®] (a mixture of natural alpha interferons made by Interferon Sciences, and available from Purdue Frederick Co., CT); α -interferon; natural alpha interferon 2a; natural alpha interferon 2b; pegylated alpha interferon 2a or 2b; consensus alpha interferon (Amgen, Inc., Newbury Park, CA); REBETRON[®] (Schering Plough, Interferon-alpha 2B + Ribavirin); pegylated interferon alpha (Reddy, K.R. et al. "Efficacy and Safety of Pegylated (40-kd) Interferon alpha-2a Compared with Interferon alpha-2a in Noncirrhotic Patients with Chronic Hepatitis C (Hepatology, 33, pp. 433-438 (2001); consensus interferon (INFERGEN[®])(Kao, J.H., et al., "Efficacy of Consensus Interferon in the Treatment of Chronic Hepatitis" J. Gastroenterol. Hepatol. 15, pp. 1418-1423 (2000); lymphoblastoid or "natural" interferon; interferon tau (Clayette, P. et al., "IFN-tau, A New Interferon Type I with Antiretroviral activity" Pathol. Biol. (Paris) 47, pp. 553-559 (1999); interleukin-2 (Davis, G.L. et al., "Future Options for the Management of Hepatitis C." Seminars in Liver Disease, 19, pp. 103-112 (1999); Interleukin-6 (Davis et al. "Future Options for the

Management of Hepatitis C." Seminars in Liver Disease 19, pp. 103-112 (1999); interleukin-12 (Davis, G.L. et al., "Future Options for the Management of Hepatitis C." Seminars in Liver Disease, 19, pp. 103-112 (1999); and compounds that enhance the development of type 1 helper T cell response (Davis et al., "Future Options for the Management of Hepatitis C." Seminars in Liver Disease, 19, pp. 103-112 (1999)). Also included are compounds that stimulate the synthesis of interferon in cells (Tazulakhova, E.B. et al., "Russian Experience in Screening, analysis, and Clinical Application of Novel Interferon Inducers" J. Interferon Cytokine Res., 21 pp. 65-73) including, but are not limited to, double stranded RNA, alone or in combination with tobramycin, and Imiquimod (3M Pharmaceuticals; Sauder, D.N. "Immunomodulatory and Pharmacologic Properties of Imiquimod" J. Am. Acad. Dermatol., 43 pp. S6-11 (2000)). In addition, known protease inhibitors (e.g., HCV protease inhibitors) can be tested for suitability with the methods described herein.

Each agent may be formulated in separate dosage forms. Alternatively, to decrease the number of dosage forms administered to a patient, each agent may be formulated together in any combination. For example, the VX-950 may be formulated in one dosage form and any additional agents may be formulated together or in another dosage form. VX-950 can be dosed, for example, before, after, or during the dosage of the additional agent.

A method according to this invention may also comprise the step of administering a cytochrome P450 monooxygenase (CYP) inhibitor. CYP inhibitors may be useful in increasing liver concentrations and/or increasing blood levels of compounds (e.g., VX-950) that are inhibited by CYP.

The advantages of improving the pharmacokinetics of a drug (e.g., by administering a CYP inhibitor) are well accepted in the art. By administering a CYP inhibitor, this invention provides for decreased metabolism of the protease inhibitor, VX-950. The pharmacokinetics of the protease inhibitor are thereby improved. The advantages of improving the pharmacokinetics of a drug are well accepted in the art. Such improvement may lead to increased blood levels of the protease inhibitor. More importantly for HCV therapies, the improvement may lead to increased concentrations of the protease inhibitor in the liver.

In a method of this invention, the amount of CYP inhibitor administered is sufficient to increase the blood levels of the VX-950 as compared to the blood levels of this protease inhibitor in the absence of a CYP inhibitor. Advantageously, in a method of this invention, an even further lower dose of protease inhibitor may be therefore used
5 (relative to administration of a protease inhibitor alone).

Accordingly, another embodiment of this invention provides a method for increasing blood levels or increasing liver concentrations of VX-950 in a patient receiving VX-950 comprising administering to the patient a therapeutically effective amount of VX-950 and a cytochrome P450 monooxygenase inhibitor.

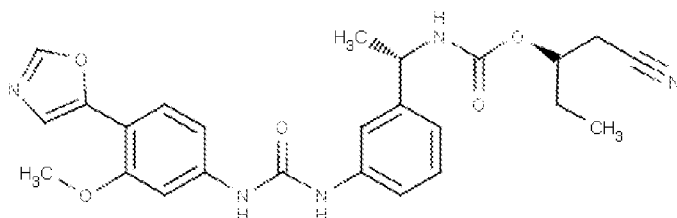
10 In addition to treating patients infected with hepatitis C, the methods of this invention may be used to prevent a patient from becoming infected with hepatitis C, e.g., a patient who may undergo a blood transfusion. Accordingly, one embodiment of this invention provides a method for preventing a hepatitis C virus infection in a patient (e.g., prophylactic treatment) comprising administering to the patient a) a formulation of VX-
15 950 or any composition according to this invention; and optionally, b) a cytochrome P450 monooxygenase inhibitor.

As would be realized by skilled practitioners, if a method of this invention is being used to treat a patient prophylactically, and that patient becomes infected with hepatitis C virus, the method may then treat the infection. Therefore, one embodiment of
20 this invention provides VX-950 or any composition according to this invention and optionally, a cytochrome P450 monooxygenase inhibitor, wherein the inhibitors of the combination are in therapeutically effective amounts for treating or preventing a hepatitis C infection in a patient.

If an embodiment of this invention involves a CYP inhibitor, any CYP inhibitor
25 that improves the pharmacokinetics of VX-950 may be used in a method of this invention. These CYP inhibitors include, but are not limited to, ritonavir (International Application WO 94/14436), ketoconazole, troleandomycin, 4-methyl pyrazole, cyclosporin, clomethiazole, cimetidine, itraconazole, fluconazole, miconazole, fluvoxamine, fluoxetine, nefazodone, sertraline, indinavir, nelfinavir, amprenavir,
30 fosamprenavir, saquinavir, lopinavir, delavirdine, erythromycin, VX-944, and VX-497. Preferred CYP inhibitors include ritonavir, ketoconazole, troleandomycin, 4-methyl

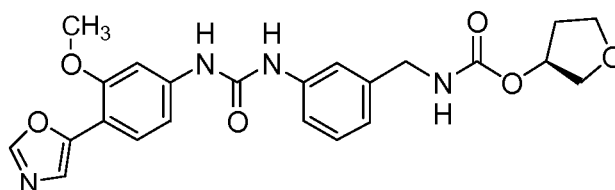
pyrazole, cyclosporin, and clomethiazole. For preferred dosage forms of ritonavir, see U.S. Pat. No. 6,037, 157, and the documents cited therein: U.S. Pat. No. 5,484,801, U.S. App. No. 08/402,690, and International Applications WO 95/07696 and WO 95/09614).

The structure of VX-944 is as follows:



VX-497 is an IMPDH inhibitor. A combination of VX-497, pegylated interferon- α (IFN- α), and ribavirin is currently in clinical development for treating HCV (W. Markland et al., (2000) *Antimicrobial & Antiviral Chemotherapy*, 44, p. 859; U.S. Pat. No. 6,541,496).

The structure of VX-497 is as follows:



VX-497

Methods for measuring the ability of a compound to inhibit cytochrome P450 monooxygenase activity are known (see U.S. Pat. No. 6,037,157 and Yun, et al. (1993) *Drug Metabolism & Disposition*, vol. 21, pp. 403-407).

A CYP inhibitor employed in this invention may be an inhibitor of only one isozyme or more than one isozyme. If the CYP inhibitor inhibits more than one isozyme, the inhibitor may nevertheless inhibit one isozyme more selectively than another isozyme. Any such CYP inhibitors may be used in a method of this invention.

In a method of this invention, the CYP inhibitor may be administered together with a formulation of VX-950 or any composition according to this invention in the same dosage form or in separate dosage forms.

If the CYP inhibitor and the other components of the combination are administered in separate dosage forms, each inhibitor may be administered about simultaneously. Alternatively, the CYP inhibitor may be administered in any time period around administration of the combination. That is, the CYP inhibitor may be administered prior to, together with, or following each component of the combination. The time period of administration should be such that the CYP inhibitor affects the metabolism of a component of the combination, preferably, of VX-950. For example, if VX-950 is administered first, the CYP inhibitor should be administered before VX-950 is substantially metabolized and/or excreted (e.g., within the half-life of VX-950).

Nucleic Acid and Protein Analysis

The genes (or their encoded polypeptides) of a signature set described herein can be used in the diagnosis of HCV, and/or in predicting the treatment outcome of a subject with HCV. Further, the levels of one or more (or all) genes (or encoded polypeptide) of the signature can be used to select a treatment regimen, select dosages of a given treatment, and/or select the duration of a treatment regimen. For example, the levels of an ISG at two or more time points (e.g., prior to treatment or within 1, 2, 3, 4, or 5 days of starting treatment and at another time(s), e.g., at least 1, 2, 3, 4, 5, or more days after the first time point or 7, 8, 9, 10, 11, 12, 13, 14 or more days after the start of treatment) can be used to predict a subject's response to a given therapy (e.g., VX-950). As another example, the pattern or levels of expression of a plurality of genes (e.g., an ISG(s)) can correlate with a given treatment regimen or outcome prediction.

Numerous methods for detecting expression of a gene (e.g., a nucleic acid and/or encoded protein of one or more genes of the signature set described herein) (e.g., an ISG), and for detecting the levels of expression, are available to the skilled artisan. The methods include hybridization-based methods for nucleic acid detection (e.g., PCR or Northern blot), and antibody-based methods for protein detection (e.g., Western blot, radioimmunoassay (RIA), or ELISA).

The expression levels of a gene of the signature set can be determined using nucleic acid or hybridization or amplification techniques known in the art (e.g., using PCR or Northern blot). The expression levels in a sample (e.g., from a subject with

hepatitis C) can be quantitatively or qualitatively compared to the levels in a reference or control (e.g., the levels in a healthy subject).

Arrays are particularly useful molecular tools for characterizing a sample, e.g., a sample from a subject, e.g., a subject with hepatitis C. For example, an array having
5 capture probes for multiple genes (or for multiple proteins), including probes for a gene(s) of the signature set described herein, can be used in a method described herein. Altered expression of a nucleic acid and/or encoded protein of the signature set described herein can be used to evaluate a sample, e.g., a sample from a subject, e.g., to predict the subject's response to treatment (e.g., treatment with VX-950).

10 Arrays can have many addresses, e.g., locatable sites, on a substrate. The featured arrays can be configured in a variety of formats, non-limiting examples of which are described below. The substrate can be opaque, translucent, or transparent. The addresses can be distributed, on the substrate in one dimension, e.g., a linear array; in two dimensions, e.g., a planar array; or in three dimensions, e.g., a three dimensional array.
15 The solid substrate may be of any convenient shape or form, e.g., square, rectangular, ovoid, or circular.

Arrays can be fabricated by a variety of methods, e.g., photolithographic methods (see, e.g., U.S. Pat. Nos. 5,143,854; 5,510,270; and 5,527,681), mechanical methods (e.g., directed-flow methods as described in U.S. Pat. No. 5,384,261), pin based methods
20 (e.g., as described in U.S. Pat. No. 5,288,514), and bead based techniques (e.g., as described in PCT US/93/04145).

The capture probe can be a single-stranded nucleic acid, a double-stranded nucleic acid (e.g., which is denatured prior to or during hybridization), or a nucleic acid having a single-stranded region and a double-stranded region. Preferably, the capture probe is
25 single-stranded. The capture probe can be selected by a variety of criteria, and preferably is designed by a computer program with optimization parameters. The capture probe can be selected to hybridize to a sequence rich (e.g., non-homopolymeric) region of the gene. The T_m of the capture probe can be optimized by prudent selection of the complementarity region and length. Ideally, the T_m of all capture probes on the array is
30 similar, e.g., within 20, 10, 5, 3, or 2°C of one another.

The isolated nucleic acid is preferably mRNA that can be isolated by routine methods, e.g., including DNase treatment to remove genomic DNA and hybridization to an oligo-dT coupled solid substrate (e.g., as described in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y.). The substrate is washed, and the mRNA is eluted.

5 The isolated mRNA can be reversed transcribed and optionally amplified, e.g., by rtPCR (e.g., as described in U.S. Pat. No. 4,683,202). The nucleic acid can be an amplification product, e.g., from PCR (U.S. Pat. Nos. 4,683,196 and 4,683,202); rolling circle amplification ("RCA," U.S. Pat. No. 5,714,320), isothermal RNA amplification or NASBA (U.S. Pat. Nos. 5,130,238; 5,409,818; and 5,554,517), and strand displacement
10 amplification (U.S. Pat. No. 5,455,166). The nucleic acid can be labeled during amplification, e.g., by the incorporation of a labeled nucleotide. Examples of preferred labels include fluorescent labels, e.g., red-fluorescent dye Cy5 (Amersham) or green-fluorescent dye Cy3 (Amersham), and chemiluminescent labels, e.g., as described in U.S. Pat. No. 4,277,437. Alternatively, the nucleic acid can be labeled with biotin, and
15 detected after hybridization with labeled streptavidin, e.g., streptavidin-phycoerythrin (Molecular Probes).

The labeled nucleic acid can be contacted to the array. In addition, a control nucleic acid or a reference nucleic acid can be contacted to the same array. The control nucleic acid or reference nucleic acid can be labeled with a label other than the sample
20 nucleic acid, e.g., one with a different emission maximum. Labeled nucleic acids can be contacted to an array under hybridization conditions. The array can be washed, and then imaged to detect fluorescence at each address of the array. The levels of expression in the control and sample nucleic acids can be compared relative to each other or to a reference value.

25 The expression level of a polypeptide encoded by a gene of the signature set can be determined using an antibody specific for the polypeptide (e.g., using a Western blot or an ELISA). The polypeptide levels in a sample (e.g., from a subject with hepatitis C) can be quantitatively or qualitatively compared to the levels in a reference or control (e.g., the levels in a healthy subject).

30 Moreover, the expression levels of multiple proteins, such as a plurality of the gene transcripts of the signature set provided herein, can be rapidly determined in parallel

using a polypeptide array having antibody capture probes for each of the polypeptides. Antibodies specific for a polypeptide can be generated as generally known in the art. The polypeptide level of a gene transcript provided herein (e.g., an ISG) can be measured in a biological sample from a subject (e.g., blood, serum, or plasma).

5 A low-density (96 well format) protein array has been developed in which proteins are spotted onto a nitrocellulose membrane (Ge (2000) *Nucleic Acids Res.* 28, e3, I-VII). A high-density protein array (100,000 samples within 222 × 222 mm) used for antibody screening was formed by spotting proteins onto polyvinylidene difluoride (PVDF) (Lucking *et al.* (1999) *Anal. Biochem.* 270:103-111). See also, e.g., Mendoza *et al.* (1999). *Biotechniques* 27:778-788; MacBeath and Schreiber (2000) *Science* 289:1760-1763; and De Wildt *et al.* (2000) *Nature Biotech.* 18:989-994. These art-known methods and others can be used to generate an array of antibodies for detecting the abundance of polypeptides (e.g., encoded by gene transcripts of the signature set) in a sample. The sample can be labeled, e.g., biotinylated, for subsequent detection with streptavidin
10 coupled to a fluorescent label. The array can then be scanned to measure binding at each address. The amount of binding in a sample can be compared to the amount of binding in a control or reference.

 The nucleic acid and polypeptide arrays of the invention can be used in wide variety of applications. For example, the arrays can be used to analyze a sample from a
20 subject (e.g., peripheral blood or tissue from a liver biopsy). The sample is compared to data obtained previously, e.g., known clinical specimens, other patient samples, a healthy (non-infected) control, or data obtained from a cohort of subjects. Further, the arrays can be used to characterize a cell culture sample, e.g., to determine a cellular state after varying a parameter, e.g., dosing a patient with an anti-HCV therapy, e.g., VX-950.

25 The expression data can be stored in a database, e.g., a relational database such as a SQL database (e.g., Oracle or Sybase database environments). The database can have multiple tables. For example, raw expression data can be stored in one table, wherein each column corresponds to a gene (e.g., a gene transcript of the signature) being assayed, e.g., an address or an array, and each row corresponds to a sample. A separate
30 table can store identifiers and sample information, e.g., the batch number of the array used, date, and other quality control information.

Expression profiles obtained from gene expression analysis on an array can be used to compare samples and/or cells in a variety of states as described in Golub *et al.* ((1999) *Science* 286:531). In one embodiment, expression (e.g., mRNA expression or protein expression) information for a gene transcript provided herein are evaluated, e.g.,
5 by comparison a reference value, e.g., a control value from a healthy subject. Reference values can also be obtained from statistical analysis, e.g., to provide a reference value for a cohort of subjects, e.g., age and gender matched subjects, e.g., normal subjects or subjects who have HCV, e.g., a particular HCV genotype or who have undergone a particular HCV therapy. Statistical similarity to a particular reference (e.g., to a reference
10 for a risk-associated cohort) or a normal cohort can be used to provide an assessment (e.g., a prediction of treatment outcome) to a subject, e.g., a subject who has been diagnosed with HCV.

Subjects suitable for treatment can also be evaluated for expression and/or activity of a gene transcript of the signature set. Subjects can be identified as suitable for
15 treatment (e.g., with VX-950 dosing), if the expression and/or activity for a particular gene transcript is elevated relative to a reference, e.g., reference value, e.g., a reference value associated with normal.

Subjects who are being administered an agent described herein (e.g., VX-950) or other treatment can be evaluated as described for expression and/or activity of a gene(s)
20 described herein. The subject can be evaluated at multiple times, e.g., at multiple times during a course of therapy, e.g., during a therapeutic regimen, and/or prior to commencement of the regimen. Treatment of the subject can be modified depending on how the subject is responding to the therapy. For example, a change in a gene's expression or activity (e.g., normalization of the signature) can be indicative of
25 responsiveness.

Particular effects mediated by an agent may show a difference (e.g., relative to an untreated subject, control subject, or other reference) that is statistically significant (e.g., P value < 0.05 or 0.02). Statistical significance can be determined by any art known method. Exemplary statistical tests include: the Students T-test, Mann Whitney U non-
30 parametric test, and Wilcoxon non-parametric statistical test. Some statistically significant relationships have a P value of less than 0.05 or 0.02 .

Methods of Evaluating Genetic Material

There are numerous methods for evaluating genetic material to provide genetic information. These methods can be used to evaluate a genetic locus that includes a gene of the signature set. The methods can be used to evaluate one or more nucleotides, e.g., a coding or non-coding region of the gene, e.g., in a regulatory region (e.g., a promoter, a region encoding an untranslated region or intron, and so forth).

Nucleic acid samples can analyzed using biophysical techniques (e.g., hybridization, electrophoresis, and so forth), sequencing, enzyme-based techniques, and combinations thereof. For example, hybridization of sample nucleic acids to nucleic acid microarrays can be used to evaluate sequences in an mRNA population and to evaluate genetic polymorphisms. Other hybridization based techniques include sequence specific primer binding (e.g., PCR or LCR); Southern analysis of DNA, e.g., genomic DNA; Northern analysis of RNA, e.g., mRNA; fluorescent probe based techniques (see, e.g., Beaudet *et al.* (2001) *Genome Res.* 11(4):600-608); and allele specific amplification. Enzymatic techniques include restriction enzyme digestion; sequencing; and single base extension (SBE). These and other techniques are well known to those skilled in the art.

Electrophoretic techniques include capillary electrophoresis and Single-Strand Conformation Polymorphism (SSCP) detection (see, e.g., Myers *et al.* (1985) *Nature* 313:495-8 and Ganguly (2002) *Hum Mutat.* 19(4):334-42). Other biophysical methods include denaturing high pressure liquid chromatography (DHPLC).

In one embodiment, allele specific amplification technology that depends on selective PCR amplification may be used to obtain genetic information. Oligonucleotides used as primers for specific amplification may carry the mutation of interest in the center of the molecule (so that amplification depends on differential hybridization) (Gibbs *et al.* (1989) *Nucl. Acids Res.* 17:2437-2448) or at the extreme 3' end of one primer where, under appropriate conditions, mismatch can prevent, or reduce polymerase extension (Prossner (1993) *Tibtech* 11:238). In addition, it is possible to introduce a restriction site in the region of the mutation to create cleavage-based detection (Gasparini *et al.* (1992) *Mol. Cell Probes* 6:1). In another embodiment, amplification can be performed using Taq ligase for amplification (Barany (1991) *Proc. Natl. Acad. Sci USA* 88:189). In such cases, ligation will occur only if there is a perfect match at the 3' end of the 5' sequence

making it possible to detect the presence of a known mutation at a specific site by looking for the presence or absence of amplification.

Enzymatic methods for detecting sequences include amplification based-methods such as the polymerase chain reaction (PCR; Saiki, *et al.* (1985) *Science* 230:1350-1354) and ligase chain reaction (LCR; Wu, *et al.* (1989) *Genomics* 4:560-569; Barringer *et al.* (1990), *Gene* 1989:117-122; F. Barany (1991) *Proc. Natl. Acad. Sci. USA* 1988:189-193); transcription-based methods utilize RNA synthesis by RNA polymerases to amplify nucleic acid (U.S. Pat. Nos. 6,066,457; 6,132,997; and 5,716,785; Sarkar *et al.*, (1989) *Science* 244:331-34; Stofler *et al.*, (1988) *Science* 239:491); NASBA (U.S. Patent Nos. 5,130,238; 5,409,818; and 5,554,517); rolling circle amplification (RCA; U.S. Pat. Nos. 5,854,033 and 6,143,495) and strand displacement amplification (SDA; U.S. Pat. Nos. 5,455,166 and 5,624,825). Amplification methods can be used in combination with other techniques.

Other enzymatic techniques include sequencing using polymerases, e.g., DNA polymerases and variations thereof such as single base extension technology. See, e.g., U.S. Pat. Nos. 6,294,336; 6,013,431; and 5,952,174.

Fluorescence based detection can also be used to detect nucleic acid polymorphisms. For example, different terminator ddNTPs can be labeled with different fluorescent dyes. A primer can be annealed near or immediately adjacent to a polymorphism, and the nucleotide at the polymorphic site can be detected by the type (e.g., "color") of the fluorescent dye that is incorporated.

Hybridization to microarrays can also be used to detect polymorphisms, including SNPs. For example, a set of different oligonucleotides, with the polymorphic nucleotide at varying positions with the oligonucleotides can be positioned on a nucleic acid array. The extent of hybridization as a function of position and hybridization to oligonucleotides specific for the other allele can be used to determine whether a particular polymorphism is present. See, e.g., U.S. Pat. No. 6,066,454.

In one implementation, hybridization probes can include one or more additional mismatches to destabilize duplex formation and sensitize the assay. The mismatch may be directly adjacent to the query position, or within 10, 7, 5, 4, 3, or 2 nucleotides of the query position. Hybridization probes can also be selected to have a particular T_m , e.g.,

between 45-60°C, 55-65°C, or 60-75°C. In a multiplex assay, T_m 's can be selected to be within 5, 3, or 2°C of each other.

It is also possible to directly sequence the nucleic acid for a particular genetic locus (e.g., a gene transcript's locus), e.g., by amplification and sequencing, or
5 amplification, cloning and sequence. High throughput automated (e.g., capillary or microchip based) sequencing apparatus can be used. In still other embodiments, the sequence of a protein of interest is analyzed to infer its genetic sequence. Methods of analyzing a protein sequence include protein sequencing, mass spectroscopy, sequence/epitope specific immunoglobulins, and protease digestion.

10 **Kits and Reagents**

One or more of the gene transcripts of the transcriptional signature described herein can be used as a component of a kit or as a reagent, e.g., a diagnostic kit or diagnostic reagent. For example, a nucleic acid (or its complement) (e.g., an oligonucleotide, e.g., probe) corresponding to one or more of the genes described herein
15 (or one or more signature sets described herein) can be a member of a nucleic acid array against which a sample (e.g., from a subject, e.g., a subject being evaluated for HCV infection) is hybridized to determine the level of gene expression. For example, a signature set described herein can be present on an array for a TAQMAN® gene expression assay (Applied Biosystems) (e.g., a custom TAQMAN® assay), e.g., for use
20 in a 384-well plate format, e.g., using standard protocols. The diagnostic evaluation of a subject's sample (e.g., peripheral blood) can be performed, e.g., in a doctor's office, hospital laboratory, or contract laboratory.

The nucleic acid can contain the full length gene transcript (or its complement), or a fragment of the transcript (or its complement) (e.g., an oligonucleotide, e.g., probe) that
25 allows for it to specifically bind to the nucleic acid complement (or the nucleic acid) in the sample under selected hybridization conditions. The level can then be compared to a control or reference value. The control or reference value can be part of the kit, or alternatively, the kit can contain the world wide web address on which reference information is located. Alternatively, nucleic acid (or its complement) corresponding to
30 one or more of the genes described herein can be provided as a reagent (e.g., diagnostic

reagent) that can be used to detect the presence and level of a gene transcript described herein. For example, the nucleic acid (or its complement) can be labeled with a detectable label and hybridized with nucleic acid from a sample. The level of hybridization can then be compared to a reference value. The reference value can be provided with the reagent, or alternatively, the reagent can contain a world wide web address for a site on which reference information is located.

Likewise, the polypeptide corresponding to a gene described herein can be used as a reagent or as a component of a kit. The polypeptide can be the full length polypeptide or a fragment thereof that allows for it to specifically bind to an antibody or a ligand (e.g., receptor ligand or binding partner or fragment thereof) that is specific for the protein from which the fragment derives, or otherwise allow specific identification of the protein. In another embodiment, antibodies (including intact and/or full length immunoglobulins of types IgA, IgG (e.g., IgG1, IgG2, IgG3, IgG4), IgE, IgD, IgM (as well as subtypes thereof) and antibody fragments, e.g., single chain antibodies, Fab fragments, F(ab')₂ fragments, Fd fragments, Fv fragments, and dAb fragments) specific for one or more polypeptides encoded by gene transcripts can be a reagent or component of a kit for the detection of the polypeptide. For example, a sample can be contacted with the antibody under conditions that allow for binding of the antibody to its antigen and the presence and/or amount of binding are then detected (e.g., by ELISA). Any of the kits can optionally include instructions for its use (e.g., how to use the kit to predict a treatment outcome or to select a treatment regimen, etc.) or can contain a world wide web address to a link where instructions are provided. The reagents may also be supplied with instructions for their use (e.g., how to use the reagents to predict a treatment outcome or to select a treatment regimen, etc.) or a world wide web address to a link where instructions are provided.

As an example, the patterns of expression of a plurality of the genes (e.g., a signature set) described herein in a sample from a subject can be compared with the patterns of expression of the same genes from references, e.g., enhanced responders or non-enhanced responders for a particular therapy (e.g., VX-950 dosing), or non-infected subjects. From the comparison, a prediction can be made, e.g., if the subject's sample has the same or similar pattern of expression of the gene transcripts as the enhanced

responder, a prediction can be made that the subject will also respond well to the given therapy. Whether a pattern or expression is the same or similar can be determined by one skilled in the art based upon knowledge of the art, and can optionally include statistical methods.

5 The kits and reagents can be used, for example, to diagnose HCV, predict the treatment outcome of a subject with HCV (e.g., if the subject is administered a particular therapy), select a treatment regimen (e.g., a monotherapy or combination therapy), select dosages of a given treatment, and/or select the duration of a treatment regimen.

Additional Uses

10 In one method, information about the subject's gene expression levels, e.g., the result of evaluating a signature set described herein (e.g., a signature set of HCV infection), is provided (e.g., communicated, e.g., electronically communicated) to a third party, e.g., a hospital, clinic, a government entity, reimbursing party or insurance company (e.g., a life insurance company). For example, choice of medical procedure,
15 payment for a medical procedure, payment by a reimbursing party, or cost for a service or insurance can be function of the information. E.g., the third party receives the information, makes a determination based at least in part on the information, and optionally communicates the information or makes a choice of procedure, payment, level of payment, coverage, etc. based on the information.

20 In one embodiment, a premium for insurance (e.g., life or medical) is evaluated as a function of information about one or more gene expression levels, e.g., a signature set described herein, e.g., a signature set of HCV infection. For example, premiums can be increased (e.g., by a certain percentage) if the genes of a signature set described herein are differentially expressed between an insured candidate (or a candidate seeking
25 insurance coverage) and a reference value (e.g., a non-HCV infected person). As another example, premiums can be decreased if levels of an ISG(s) are sustained (as described herein) after treatment with a viral protease inhibitor (e.g., VX-950) in the an HCV-infected insured candidate or an HCV-infected candidate seeking insurance coverage. Premiums can also be scaled depending on gene expression levels, e.g., the result of
30 evaluating a signature set described herein (e.g., a signature set of HCV infection). For

example, premiums can be assessed to distribute risk, e.g., as a function of gene expression levels, e.g., the result of evaluating a signature set described herein (e.g., a signature set of HCV infection). In another example, premiums are assessed as a function of actuarial data that is obtained from subjects that are enhanced or non-enhanced responders.

Information about gene expression levels, e.g., the result of evaluating a signature set described herein (e.g., a signature set of HCV infection), can be used, e.g., in an underwriting process for life insurance. The information can be incorporated into a profile about a subject. Other information in the profile can include, for example, date of birth, gender, marital status, banking information, credit information, children, and so forth. An insurance policy can be recommended as a function of the information on gene expression levels, e.g., the result of evaluating a signature set described herein (e.g., a signature set of HCV infection), along with one or more other items of information in the profile. An insurance premium or risk assessment can also be evaluated as function of the signature set information. In one implementation, points are assigned on the basis of being an enhanced or non-enhanced responder.

In one embodiment, information about gene expression levels, e.g., the result of evaluating a signature set described herein (e.g., a signature set of HCV infection), is analyzed by a function that determines whether to authorize the transfer of funds to pay for a service or treatment provided to a subject (or make another decision referred to herein). For example, the results of analyzing a signature set described herein may indicate that a subject is a non-enhanced responder, suggesting that a longer treatment course is needed, thereby triggering an outcome that indicates or causes authorization to pay for a service or treatment (e.g., a longer duration of anti-HCV therapy, e.g., VX-950 therapy) provided to a subject. For example, an entity, e.g., a hospital, care giver, government entity, or an insurance company or other entity which pays for, or reimburses medical expenses, can use the outcome of a method described herein to determine whether a party, e.g., a party other than the subject patient, will pay for services (e.g., a particular monotherapy or combination therapy, and/or a certain duration of therapy) or treatment provided to the patient. For example, a first entity, e.g., an insurance company, can use the outcome of a method described herein to determine whether to provide

financial payment to, or on behalf of, a patient, e.g., whether to reimburse a third party, e.g., a vendor of goods or services, a hospital, physician, or other care-giver, for a service or treatment provided to a patient. For example, a first entity, e.g., an insurance company, can use the outcome of a method described herein to determine whether to
5 continue, discontinue, enroll an individual in an insurance plan or program, e.g., a health insurance or life insurance plan or program.

EXAMPLES

Experiments were performed, in part, to identify a minimal set of gene transcripts associated with chronic HCV infection in clinical samples, establish a baseline gene
10 expression data set (e.g., signature set) in the peripheral blood that may include genes to monitor and correlate with treatment outcomes, and determine if the anti-viral activity of VX-950 results in changes in gene expression in the peripheral blood cells coincident with viral clearance in plasma.

A comparison of baseline peripheral blood samples from healthy and HCV
15 subjects identified a robust, statistically significant set of 258 genes (a signature set) associated with HCV infection (5% false discovery rate). A subset of expression changes in HCV infected patients were of fairly large magnitude (2-fold to 5-fold) and reflected the regulation of genes that have previously been shown to be associated with host antiviral response. Following dosing with VX-950 for 14 days, the expression of these
20 genes tended to normalize towards levels seen in healthy subjects, indicating that VX-950 normalized the signature set, and led to a median 4.4-log drop in HCV plasma viral load (e.g., in subjects dosed with 750 mg VX-950). Sustained levels of interferon-sensitive genes (ISGs) in peripheral blood during VX-950 dosing were associated with an enhanced antiviral response.

Without being bound by theory, it appears that inhibition of NS3/4A by VX-950
25 may restore IFN signaling, block viral replication in hepatocytes, and block cleavage of TRIF/CARDIF, thereby restoring IRF3 & RIG-1 signaling and transcription of ISGs which activate intrinsic anti-viral defenses, including production of IFN β , in hepatocytes. Further, it is believed, with respect to plasma clearance of HCV RNA, that B-cells,
30 monocytes, and dendritic cells may take up and degrade HCV particles, and degradation

releases viral proteins and dsRNA that activate gene expression in peripheral blood cells. Clearance of plasma HCV RNA and elimination of virus particles can result in normalization of the gene expression signature. In contrast, gene expression persists (e.g., and no normalization occurs) in the presence of 2-3 logs of plasma HCV RNA. Finally, it appears that sustained expression of ISGs in subjects who clear plasma HCV RNA may reflect restored intrinsic antiviral defenses and secretion of interferons. The sustained expression of ISGs may be a sign of the re-emergence of an effective immune response that is essential to eliminate residual HCV infected hepatocytes. Thus, expression of ISGs and other genes associated with acquired immunity may be monitored to establish potential correlations with treatment outcomes.

Example 1: Materials and Methods

The studies presented herein included four panels, each of six healthy subjects, administered placebo, 450 q8h, or 750 q8h, or 1250 mg q12h VX-950 for 5 days and four panels of subjects with HCV administered placebo (six subjects), 450 (ten subjects) q8h, or 750 VX-950 (eight subjects) q8h, or 1250 mg (ten subjects) q12h for 14 days.

RNA Isolation: Peripheral whole blood (2.5 ml) was collected pre-dose and on day-5 from healthy subjects and pre-dose, day-7, -14 and at follow-up from HCV subjects. Total RNA was isolated using standard using PAXGENE BLOOD RNA™ tubes and protocols (Qiagen). Globin transcripts were reduced using the GLOBINCLEAR™ Human Globin mRNA Removal Kit (Ambion).

Transcriptional Analysis: Transcriptional analyses were performed using Affymetrix U133 v2.0 gene arrays after globin reduction. RNA was prepared using standard protocols and hybridized to Affymetrix Human Genome U133 plus 2.0 arrays.

Data Analysis: Data was processed using Bioconductor, a software, primarily based on R programming language for the analysis and comprehension of genomic data (Bioconductor.org). The data was preprocessed using GCRMA package in Bioconductor, which normalizes at the probe level using the GC content of probes in normalization with RMA (robust multi-array).

Statistically significant differentially expressed genes were identified using SAM algorithm (Significance Analysis of Microarrays) with a false discovery rate of 5%.

Clustering: The statistically significant differentially expressed genes were then subjected to hierarchical (agglomerative) clustering of both genes and subjects using Bioconductor “heatmap” function to identify the minimal set that will distinguish between the two groups.

Example 2: Demographics of HCV Infected Subjects

The study of subjects with chronic HCV infections included six subjects who received a placebo, ten subjects who were dosed with VX-950 at 450mg q8h, eight subjects who were dosed with VX-950 at 750mg q8h, and ten subjects who were dosed with VX-950 at 1250mg q12h. Subject demographics were comparable among groups, except that there were more females in the 750 mg dose group. Only 5 of 28 subjects who received VX-950 had not received prior therapy for HCV. The subject demographics are shown in Table 1.

Table 1: Subject Demographics:

	placebo (n=6)	450 mg q8h (n=10)	750 mg q8h (n=8)	1250 mg q12h (n=10)
Male/female	3/3	8/2	3/5	8/2
Median age (yr)	53	47	52	44
Median wt (kg)	77.2	78.5	75.0	70.0
Treatment-naïve	2	1	1	3
Median				
HCV RNA (log ₁₀)*	6.38	6.45	6.13	6.48
Mean				
HCV RNA (log ₁₀)*	6.28	6.54	6.18	6.46

*: HCV RNA levels were determined by the COBAS AmpliPrep/COBAS TAQMAN™ HCV Test (Roche Molecular Diagnostics).

Example 3: VX-950 Treatment Reduces HCV Viral Loads

The HCV viral loads in HCV infected subjects were examined in each of the groups described in Example 2. As shown in FIG. 1, subjects on placebo had no significant change in viral load (open circles), while all VX-950 dosed subjects had a >2-log initial drop in viral load. All dose groups showed a steep decline of RNA levels in the first 2-3 days. After the initial steep decline over the 3 days, a slower rate of RNA decline was observed in the 750 mg dose group (diamonds), but the median HCV RNA

was still decreasing at the end of 14 days. In this assay, for the 450 mg (squares) and 1250 mg (triangles) dose groups, the RNA levels remain more or less stable and even had a tendency to increase again.

Example 4: Signature set of HCV Infection

Hierarchical clustering analysis revealed a signature set associated with chronic HCV infection. A comparison of genes that are differentially expressed between healthy and HCV-infected subjects at the pre-dose time point revealed a signature set of HCV infection. This signature set consists of 258 genes associated with chronic HCV infection ($\text{FDR} < 5\%$). The signature set of 258 was identified at baseline, i.e., before the onset of VX-950 dosing. Further, on dosing with VX-950, the expression levels in the HCV-infected patients resolved towards healthy levels, as described in Example 5.

The full list of 258 genes, including the Affymetrix probeset ID, gene symbol, gene description, GO (gene ontology) biological process, GL molecular function, and GL cellular component, is provided in Table 2.

Table 2: Genes of an HCV Signature Set

Affymetrix probeset ID	Gene Symbol	Gene Description	GO Biological Process	GO Molecular Function	GO Cellular Component
1557961_s_at	---	---	---	---	---
227353_at	---	---	---	---	---
228412_at	---	Full-Length Cdna Clone Cs0Df004Yg03 Of Fetal Brain Of Homo Sapiens (Human)	---	---	---
228549_at	---	---	---	---	---
228758_at	---	Hypothetical Loc389185	---	---	---
232253_at	---	Hypothetical Gene Supported By Ak128882	---	---	---
238768_at	---	Hypothetical Loc388969	---	---	---
204567_s_at	ABCG1	Atp-Binding Cassette, Sub- Family G (White), Member 1	Lipid Transport /// Cholesterol Metabolism /// Detection Of Hormone Stimulus /// Response To Organic Substance /// Cholesterol Homeostasis /// Transport /// Lipid Transport /// Transport	Nucleotide Binding /// Atp Binding /// L- Tryptophan Transporter Activity /// Purine Nucleotide Transporter Activity /// Permease Activity /// Atpase Activity /// Atpase Activity, Coupled To Transmembrane Movement Of Substances /// Protein Dimerization Activity /// Atp Binding /// Nucleoside- Triphosphatase Activity /// Atpase Activity, Coupled To Transmembrane Movement Of Substances /// Atpase Activity, Coupled To Transmembrane Movement Of Substances	Membrane Fraction /// Endoplasmic Reticulum /// Golgi Stack /// Membrane /// Integral To Membrane /// Integral To Plasma Membrane
213017_at	ABHD3	Abhydrolase Domain Containing 3	---	Catalytic Activity /// Hydrolase Activity	---
202323_s_at	ACBD3	Acyl-Coenzyme A Binding Domain Containing 3	Steroid Biosynthesis /// Intracellular Protein Transport /// Lipid Biosynthesis	Acyl-Coa Binding /// Protein Carrier Activity	Mitochondrion /// Golgi Stack /// Membrane

<i>Affymetrix probeset ID</i>	<i>Gene Symbol</i>	<i>Gene Description</i>	<i>GO Biological Process</i>	<i>GO Molecular Function</i>	<i>GO Cellular Component</i>
201786_s_at	ADAR	Adenosine Deaminase, Rna-Specific	Mrna Processing /// Rna Editing /// Antimicrobial Humoral Response (Sensu Vertebrata) /// Base Conversion Or Substitution Editing /// Rna Processing	Dna Binding /// Double-Stranded Rna Binding /// Double-Stranded Rna Adenosine Deaminase Activity /// Hydrolase Activity /// Metal Ion Binding /// Double-Stranded Rna Adenosine Deaminase Activity /// Rna Binding /// Double-Stranded Rna Adenosine Deaminase Activity /// Adenosine Deaminase Activity /// Zinc Ion Binding /// Double-Stranded Rna Adenosine Deaminase Activity	Nucleus /// Cytoplasm /// Intracellular /// Nucleus
239171_at	ADD3	Adducin 3 (Gamma)	---	Structural Constituent Of Cytoskeleton /// Calmodulin Binding	Cytoskeleton /// Membrane /// Membrane
202912_at	ADM	Adrenomedullin	Camp Biosynthesis /// Progesterone Biosynthesis /// Signal Transduction /// Cell-Cell Signaling /// Pregnancy /// Excretion /// Circulation /// Response To Wounding	Hormone Activity /// Receptor Binding	Extracellular Space /// Soluble Fraction /// Extracellular Region
200849_s_at	AHCYL1	S-Adenosylhomocysteine Hydrolase-Like 1	One-Carbon Compound Metabolism	Adenosylhomocysteinase Activity /// Hydrolase Activity	---
225555_x_at	AKIP	Aurora Kinase A Interacting Protein 1	Negative Regulation Of Mitosis /// Positive Regulation Of Proteolysis	Protein Binding	Nucleus /// Nucleus

<i>Affymetrix probeset ID</i>	<i>Gene Symbol</i>	<i>Gene Description</i>	<i>GO Biological Process</i>	<i>GO Molecular Function</i>	<i>GO Cellular Component</i>
222715_s_at	AP1GBP1	Ap1 Gamma Subunit Binding Protein 1	Intracellular Protein Transport /// Endocytosis /// Transport /// Protein Transport	Calcium Ion Binding	Golgi Stack /// Membrane /// Ap-1 Adaptor Complex /// Cytoplasm /// Golgi Apparatus
209870_s_at	APBA2	Amyloid Beta (A4) Precursor Protein-Binding, Family A, Member 2 (X11-Like)	Nervous System Development /// Protein Transport /// Transport	Protein Binding /// Protein Binding	---
228520_s_at	APLP2	Amyloid Beta (A4) Precursor-Like Protein 2	G-Protein Coupled Receptor Protein Signaling Pathway	Dna Binding /// Serine-Type Endopeptidase Inhibitor Activity /// Protein Binding /// Dna Binding /// Endopeptidase Inhibitor Activity /// Binding	Nucleus /// Integral To Membrane /// Nucleus /// Integral To Membrane
221653_x_at	APOL2	Apolipoprotein L, 2	Lipid Metabolism /// Lipid Transport /// Acute-Phase Response /// Development /// Cholesterol Metabolism /// Lipoprotein Metabolism /// Transport	Receptor Binding /// High-Density Lipoprotein Binding /// Lipid Binding /// Lipid Binding	Extracellular Region /// Intracellular
225707_at	ARL6IP6	Adp-Ribosylation-Like Factor 6 Interacting Protein 6	---	---	---

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209824_s_at	ARNTL	Aryl Hydrocarbon Receptor Nuclear Translocator- Like	Regulation Of Transcriptio n, Dna- Dependent /// Signal Transductio n /// Circadian Rhythm /// Transcriptio n /// Regulation Of Transcriptio n	Transcription Factor Activity /// Signal Transducer Activity /// Dna Binding /// Transcription Regulator Activity /// Receptor Activity	Nucleus
208836_at	ATP1B3	Atpase, Na+/K+ Transporting, Beta 3 Polypeptide	Transport /// Potassium Ion Transport /// Sodium Ion Transport	Sodium:Potassium- Exchanging Atpase Activity /// Potassium Ion Binding /// Sodium Ion Binding /// Sodium:Potassium- Exchanging Atpase Activity	Sodium:Potassium- Exchanging Atpase Complex /// Membrane /// Integral To Membrane
214149_s_at	ATP6V0E	Atpase, H+ Transporting, Lysosomal 9Kda, V0 Subunit E	Ion Transport /// Atp Synthesis Coupled Proton Transport /// Proton Transport /// Transport /// Proton Transport	Transporter Activity /// Hydrolase Activity /// Hydrogen-Transporting Atp Synthase Activity, Rotational Mechanism /// Hydrogen- Transporting Atpase Activity, Rotational Mechanism /// Hydrogen Ion Transporter Activity /// Hydrogen- Transporting Atpase Activity, Rotational Mechanism	Membrane Fraction /// Proton- Transporting Two-Sector Atpase Complex /// Integral To Membrane
236307_at	BACH2	Btb And Cnc Homology 1, Basic Leucine Zipper Transcription Factor 2	Transcriptio n /// Regulation Of Transcriptio n, Dna- Dependent	Dna Binding /// Protein Binding	Nucleus

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203140_at	BCL6	B-Cell ClI/Lymphoma 6 (Zinc Finger Protein 51) /// B- Cell ClI/Lymphoma 6 (Zinc Finger Protein 51)	Negative Regulation Of Transcription From Rna Polymerase Ii Promoter /// Transcription /// Regulation Of Transcription, Dna- Dependent /// Inflammatory Response /// Positive Regulation Of Cell Proliferation /// Regulation Of Transcription, Dna- Dependent	Transcription Factor Activity /// Protein Binding /// Zinc Ion Binding /// Metal Ion Binding /// Nucleic Acid Binding /// Dna Binding /// Protein Binding	Mediator Complex /// Nucleus /// Nucleus
228617_at	BIRC4BP	Xiap Associated Factor-1	---	Zinc Ion Binding	---
243509_at	BTG1	B-Cell Translocation Gene 1, Anti- Proliferative	Spermatid Development /// Negative Regulation Of Cell Proliferation /// Cell Migration /// Negative Regulation Of Cell Growth /// Regulation Of Apoptosis /// Positive Regulation Of Enzyme Activity /// Regulation Of Transcription /// Positive Regulation Of Endothelial Cell Differentiation /// Positive Regulation Of Myoblast Differentiation /// Positive Regulation Of Angiogenesis	Transcription Cofactor Activity /// Kinase Binding /// Protein Binding /// Enzyme Binding	Nucleus /// Nucleus /// Cytoplasm
203944_x_at	BTN2A1	Butyrophilin, Subfamily 2, Member A1	Lipid Metabolism	---	Integral To Membrane /// Integral To Plasma Membrane
205298_s_at	BTN2A2	Butyrophilin, Subfamily 2, Member A2	---	---	Integral To Membrane
201457_x_at	BUB3	Bub3 Budding Uninhibited By Benzimidazoles 3 Homolog (Yeast)	Mitosis /// Mitotic Spindle Checkpoint /// Cell Proliferation /// Mitotic Checkpoint	---	Kinetochore /// Nucleus

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222464_s_at	C10orf119	Chromosome 10 Open Reading Frame 119	---	---	---
219471_at	C13orf18	Chromosome 13 Open Reading Frame 18	---	Protein Phosphatase Inhibitor Activity	---
222458_s_at	C1orf108	Chromosome 1 Open Reading Frame 108	---	---	---
212003_at	C1orf144	Chromosome 1 Open Reading Frame 144	---	---	---
217835_x_at	C20orf24	Chromosome 20 Open Reading Frame 24	---	---	---
216032_s_at	C20orf47	Chromosome 20 Open Reading Frame 47	---	---	Integral To Membrane
223145_s_at	C6orf166	Chromosome 6 Open Reading Frame 166	---	---	---
243271_at	C7orf6	Sterile Alpha Motif Domain Containing 9Like	---	---	---
207181_s_at	CASP7	Caspase 7, Apoptosis- Related Cysteine Peptidase	Proteolysis /// Apoptotic Program /// Apoptosis /// Apoptosis	Protein Binding /// Peptidase Activity /// Cysteine-Type Peptidase Activity /// Caspase Activity /// Cysteine-Type Peptidase Activity /// Hydrolase Activity	Cytoplasm
				Rhodopsin-Like Receptor Activity /// Receptor Activity /// Protein Binding /// C-C Chemokine Receptor Activity /// Signal Transducer Activity /// G-Protein Coupled Receptor Activity /// Chemokine Receptor Activity	Plasma Membrane /// Integral To Plasma Membrane /// Integral To Membrane /// Plasma Membrane

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205098_at	CCR1	Chemokine (C-C Motif) Receptor 1	Chemotaxis /// Inflammatory Response /// Cell Adhesion /// G-Protein Signaling, Coupled To Cyclic Nucleotide Second Messenger /// Elevation Of Cytosolic Calcium Ion Concentration /// Cell-Cell Signaling /// Cytokine And Chemokine Mediated Signaling Pathway /// Signal Transduction /// GProtein Coupled Receptor Protein Signaling Pathway /// Chemotaxis /// Immune Response /// Cell Surface Receptor Linked Signal Transduction /// Response To Wounding		
203547_at	CD4	Cd4 Antigen (P55) /// Cd4 Antigen (P55)	Immune Response /// Cell Adhesion /// Transmembrane Receptor Protein Tyrosine Kinase Signaling Pathway /// T Cell Differentiation /// T Cell Selection /// Positive Regulation Of Interleukin-2 Biosynthesis /// Immune Response /// Signal Transduction /// Cell Surface Receptor Linked Signal Transduction /// Enzyme Linked Receptor Protein Signaling Pathway	Transmembrane Receptor Activity /// Coreceptor Activity /// Mhc Class Ii Protein Binding /// Protein Binding /// Zinc Ion Binding /// Receptor Activity /// Coreceptor Activity /// Receptor Activity	Plasma Membrane /// Integral To Membrane /// T Cell Receptor Complex /// Plasma Membrane /// Membrane

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209287_s_at	CDC42EP3	Cdc42 Effector Protein (Rho Gtpase Binding) 3	Regulation Of Cell Shape	---	Cytoskeleton
212501_at	CEBPB	Ccaat/Enhancer Binding Protein (C/Ebp), Beta	Transcription /// Regulation Of Transcription, Dna-Dependent /// Transcription From Rna Polymerase Ii Promoter /// Acute-Phase Response /// Inflammatory Response /// Immune Response	Transcription Factor Activity /// Dna Binding /// Dna Binding	Nucleus /// Nucleus
205212_s_at	CENTB1	Centaurin, Beta 1	Intracellular Signaling Cascade /// Regulation Of Gtpase Activity /// Signal Transduction	Phospholipase C Activity /// Gtpase Activator Activity /// Metal Ion Binding /// Zinc Ion Binding	---
205212_s_at	CENTB1	Centaurin, Beta 1	Intracellular Signaling Cascade /// Regulation Of Gtpase Activity /// Signal Transduction	Phospholipase C Activity /// Gtpase Activator Activity /// Metal Ion Binding /// Zinc Ion Binding	---
234562_x_at	CKLFSF8	Chemokine-Like Factor Superfamily 8	Chemotaxis /// Sensory Perception	Cytokine Activity	Extracellular Space /// Membrane /// Integral To Membrane
206207_at	CLC	Charcot-Leyden Crystal Protein /// Charcot-Leyden Crystal Protein	Phospholipid Metabolism /// Development /// Lipid Catabolism /// Antimicrobial Humoral Response (Sensu Vertebrata)	Lysophospholipase Activity /// Serine Esterase Activity /// Sugar Binding ///Hydrolase Activity	---

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202160_at	CREBBP	Creb Binding Protein (Rubinstein-Taybi Syndrome)	Response To Hypoxia /// Regulation Of Transcription, Dna-Dependent /// Protein Complex Assembly /// Signal Transduction /// Homeostasis /// Transcription /// Regulation Of Transcription, Dna-Dependent /// Regulation Of Transcription /// Signal Transduction /// Regulation Of Transcription	Transcription Factor Activity /// Transcription Coactivator Activity /// Histone Acetyltransferase Activity /// Signal Transducer Activity /// Protein Binding /// Zinc Ion Binding /// Transferase Activity /// Metal Ion Binding /// Protein Binding /// Transcription Cofactor Activity /// Transcription Coactivator Activity /// Protein Binding /// Transcription Coactivator Activity	Nucleus /// Cytoplasm /// Nucleus
212180_at	CRKL	V-Crk Sarcoma Virus Ct10 Oncogene Homolog (Avian)-Like	Protein Amino Acid Phosphorylation /// Cell Motility /// Intracellular Signaling Cascade /// Jnk Cascade /// Ras Protein Signal Transduction /// Intracellular Signaling Cascade	Protein-Tyrosine Kinase Activity /// Sh3/Sh2 Adaptor Activity /// Protein Binding /// Signal Transducer Activity	---
214743_at	CUTL1	Cut-Like 1, Ccaat Displacement Protein (Drosophila)	Negative Regulation Of Transcription From Rna Polymerase Ii Promoter /// Transcription /// Development /// Regulation Of Transcription, Dna-Dependent /// Development /// Regulation Of Transcription From Rna Polymerase Ii Promoter	Transcription Factor Activity /// Rna Polymerase Ii Transcription Factor Activity /// Dna Binding	Nucleus

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214743_at	CUTL1	Cut-Like 1, Ccaat Displacement Protein (Drosophila)	Negative Regulation Of Transcription From Rna Polymerase Ii Promoter /// Transcription /// Development /// Regulation Of Transcription, Dna-Dependent /// Development /// Regulation Of Transcription From Rna Polymerase Ii Promoter	Transcription Factor Activity /// Rna Polymerase Ii Transcription Factor Activity /// Dna Binding	Nucleus
209164_s_at	CYB561	Cytochrome B-561	Electron Transport /// Transport /// Generation Of Precursor Metabolites And Energy	Cytochrome-B5 Reductase Activity /// Iron Ion Binding /// Metal Ion Binding	Integral To Plasma Membrane /// Integral To Membrane
221903_s_at	CYLD	Cylindromatosis (Turban Tumor Syndrome)	Ubiquitin-Dependent Protein Catabolism /// Ubiquitin Cycle /// Cell Cycle /// Negative Regulation Of Progression Through Cell Cycle /// Ubiquitin-Dependent Protein Catabolism	Cysteine-Type Endopeptidase Activity /// Ubiquitin Thiolesterase Activity /// Ubiquitin Thiolesterase Activity /// Peptidase Activity /// Cysteine-Type Peptidase Activity /// Hydrolase Activity	Cytoskeleton
200794_x_at	DAZAP2	Daz Associated Protein 2	---	---	---
209782_s_at	DBP	D Site Of Albumin Promoter (Albumin D-Box) Binding Protein	Transcription /// Regulation Of Transcription From Rna Polymerase Ii Promoter /// Rhythmic Process /// Regulation Of Transcription, Dna-Dependent	Dna Binding /// Rna Polymerase Ii Transcription Factor Activity	Nucleus

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224009_x_at	DHRS9	Dehydrogenase/Reductase (Sdr Family) Member 9	Androgen Metabolism /// Progesterone Metabolism /// 9-Cis-Retinoic Acid Biosynthesis /// Metabolism /// Epithelial Cell Differentiation /// Retinol Metabolism /// Androgen Metabolism /// Epithelial Cell Differentiation /// Retinol Metabolism /// 9-Cis-Retinoic Acid Biosynthesis	Alcohol Dehydrogenase Activity /// Retinol Dehydrogenase Activity /// 3-Alpha(17-Beta)-Hydroxysteroid Dehydrogenase (Nad+) Activity /// Oxidoreductase Activity /// Racemase And Epimerase Activity /// Alcohol Dehydrogenase Activity /// Retinol Dehydrogenase Activity /// 3-Alpha(17-Beta)-Hydroxysteroid Dehydrogenase (Nad+) Activity	Microsome /// Integral To Endoplasmic Reticulum Membrane /// Membrane /// Microsome /// Integral To Endoplasmic Reticulum Membrane
208810_at	DNAJB6	Dnaj (Hsp40) Homolog, Subfamily B, Member 6	Protein Folding /// Response To Unfolded Protein	Heat Shock Protein Binding /// Unfolded Protein Binding	---
209188_x_at	DR1	Down-Regulator Of Transcription 1, TbpBinding (Negative Cofactor 2)	Negative Regulation Of Transcription From Rna Polymerase Ii Promoter /// Transcription /// Regulation Of Transcription, Dna-Dependent	Dna Binding /// Transcription Corepressor Activity /// Transcription Factor Binding /// Dna Binding	Nucleus
225415_at	DTX3L	Deltex 3-Like (Drosophila)	Protein Ubiquitination	Ubiquitin-Protein Ligase Activity /// Zinc Ion Binding /// Metal Ion Binding	Ubiquitin Ligase Complex
208891_at	DUSP6	Dual Specificity Phosphatase 6	Regulation Of Progression Through Cell Cycle /// Inactivation Of Mapk Activity /// Protein Amino Acid Dephosphorylation /// Protein Amino Acid Dephosphorylation	Protein Serine/Threonine Phosphatase Activity /// Protein Tyrosine Phosphatase Activity /// Hydrolase Activity /// Map Kinase Phosphatase Activity /// Phosphoprotein Phosphatase Activity /// Protein Tyrosine/Serine/Threonine Phosphatase Activity	Soluble Fraction /// Cytoplasm
212830_at	EGFL5	Egf-Like-Domain, Multiple 5	---	Structural Molecule Activity /// Calcium Ion Binding	Integral To Membrane

Affymetrix probeset ID	Gene Symbol	Gene Description	GO Biological Process	GO Molecular Function	GO Cellular Component
221497_x_at	EGLN1	Egl Nine Homolog 1 (C. Elegans)	Protein Metabolism	Iron Ion Binding /// Oxidoreductase Activity /// Oxidoreductase Activity, Acting On Single Donors With Incorporation Of Molecular Oxygen, Incorporation Of Two Atoms Of Oxygen /// Oxidoreductase Activity, Acting On Paired Donors, With Incorporation Or Reduction Of Molecular Oxygen, 2-Oxoglutarate As One Donor, And Incorporation Of One Atom Each Of Oxygen Into Both Donors /// L-Ascorbic Acid Binding /// Metal Ion Binding /// Zinc Ion Binding	Cytosol
214805_at	EIF4A1	Eukaryotic Translation Initiation Factor 4A, Isoform 1	Protein Biosynthesis	Nucleotide Binding /// Dna Binding /// Rna Binding /// Translation Initiation Factor Activity /// Protein Binding /// Atp Binding /// Atp-Dependent Helicase Activity /// Hydrolase Activity /// Nucleic Acid Binding /// Helicase Activity	---
213579_s_at	EP300	E1A Binding Protein P300	Response To Hypoxia /// Regulation Of Transcription, Dna-Dependent /// Apoptosis /// Cell Cycle /// Signal Transduction /// Nervous System Development /// Homeostasis /// Regulation Of Transcription /// Transcription /// Regulation Of Transcription	Transcription Factor Activity /// Transcription Coactivator Activity /// Histone Acetyltransferase Activity /// Protein C-Terminus Binding /// Zinc Ion Binding /// Transferase Activity /// Metal Ion Binding /// Protein Binding /// Transcription Factor Binding /// Dna Binding /// Transcription Cofactor Activity /// Transcription Coactivator Activity /// Protein Binding /// Transcription Coactivator Activity	Nucleus /// Nucleus
229966_at	EWSR1	Ewing Sarcoma Breakpoint Region 1	Transcription /// Regulation Of Transcription, Dna-Dependent	Nucleotide Binding /// Rna Binding /// Calmodulin Binding /// Zinc Ion Binding /// Metal Ion Binding /// Nucleic Acid Binding /// Rna Binding /// Dna Binding /// Transcription Factor Activity	Nucleus

<i>Affymetrix probeset ID</i>	<i>Gene Symbol</i>	<i>Gene Description</i>	<i>GO Biological Process</i>	<i>GO Molecular Function</i>	<i>GO Cellular Component</i>
215206_at	EXT1	Exostoses (Multiple) 1	Skeletal Development /// Glycosaminoglycan Biosynthesis /// Cell Cycle /// Signal Transduction /// Heparan Sulfate Proteoglycan Biosynthesis /// Negative Regulation Of Progression Through Cell Cycle	Transferase Activity, Transferring Glycosyl Groups /// Glucuronosyl-N- Acetylglucosaminyl- Proteoglycan 4-Alpha-N- Acetylglucosaminyltransferase Activity /// N- Acetylglucosaminyl- Proteoglycan 4-Beta- Glucuronosyltransferase Activity /// Transferase Activity /// N-Acetylglucosaminyl- Proteoglycan 4-Beta- Glucuronosyltransferase Activity	Endoplasmic Reticulum Membrane /// Golgi Stack /// Membrane /// Integral To Membrane /// Integral To Endoplasmic Reticulum Membrane /// Endoplasmic Reticulum /// Integral To Membrane /// Endoplasmic Reticulum /// Golgi Apparatus
224840_at	FKBP5	Fk506 Binding Protein 5	Protein Folding /// ProteinFolding	Peptidyl-Prolyl Cis-Trans Isomerase Activity /// Fk506 Binding /// Isomerase Activity /// Unfolded Protein Binding /// Protein Binding /// Binding	Nucleus
218999_at	FLJ11000	Hypothetical Protein Fij11000	---	---	---
218035_s_at	FLJ20273	Rna-Binding Protein	---	Nucleotide Binding /// Nucleic Acid Binding /// Rna Binding	---
219717_at	FLJ20280	Hypothetical Protein Fij20280	---	---	---
222751_at	FLJ22313	Hypothetical Protein Fij22313	Protein Modification	---	---
219359_at	FLJ22635	Hypothetical Protein Fij22635	---	---	---
230012_at	FLJ34790	Hypothetical Protein Fij34790	---	---	---
211074_at	FOLR1	Folate Receptor 1 (Adult) /// Folate Receptor 1 (Adult)	Receptor Mediated Endocytosis /// Folic Acid Transport	Receptor Activity /// Folic Acid Binding /// Receptor Activity /// Folic Acid Binding	Membrane Fraction /// Integral To Plasma Membrane /// Membrane

<i>Affymetrix probeset ID</i>	<i>Gene Symbol</i>	<i>Gene Description</i>	<i>GO Biological Process</i>	<i>GO Molecular Function</i>	<i>GO Cellular Component</i>
209189_at	FOS	V-Fos Fbj Murine Osteosarcoma Viral Oncogene Homolog	Dna Methylation /// Regulation Of Transcription From Rna Polymerase Ii Promoter /// Inflammatory Response /// Regulation Of Transcription, Dna- Dependent	Dna Binding /// Specific Rna Polymerase Ii Transcription Factor Activity	Nucleus /// Nucleus
228188_at	FOSL2	Fos-Like Antigen 2	Regulation Of Transcription From Rna Polymerase Ii Promoter /// Cell Death /// Regulation Of Transcription, Dna- Dependent	Transcription Factor Activity /// Dna Binding	Nucleus /// Nucleus
200959_at	FUS	Fusion (Involved In T(12;16) In Malignant Liposarcoma)	Immune Response	Nucleotide Binding /// Dna Binding /// Rna Binding /// Protein Binding /// Zinc Ion Binding /// Metal Ion Binding /// Nucleic Acid Binding /// Rna Binding /// Tumor Necrosis Factor Receptor Binding	Nucleus /// Nucleus /// Membrane
205483_s_at	G1P2	Interferon, Alpha-Inducible Protein (Clone Ifi-15K)	Protein Modification /// Immune Response /// Cell-Cell Signaling	Protein Binding	Extracellular Space /// Cytoplasm
204415_at	G1P3	Interferon, Alpha-Inducible Protein (Clone Ifi-6-16)	Immune Response /// Response To Pest, Pathogen Or Parasite /// Immune Response	---	Integral To Membrane
212804_s_at	GAPVD1	Gtpase Activating Protein And Vps9 Domains 1	---	---	---
209604_s_at	GATA3	Gata Binding Protein 3	Transcription /// Regulation Of Transcription, Dna- Dependent /// Transcription From Rna Polymerase Ii Promoter /// Defense Response /// Sensory Perception Of Sound /// Morphogenesis	Transcription Factor Activity /// Metal Ion Binding /// Dna Binding /// Transcription Factor Activity /// Zinc Ion Binding /// Dna Binding	Nucleus
235574_at	GBP4	Guanylate Binding Protein 4	Immune Response	Gtpase Activity /// Gtp Binding /// Nucleotide Binding	---

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203925_at	GCLM	Glutamate-Cysteine Ligase, Modifier Subunit	Cysteine Metabolism /// Glutathione Biosynthesis	Glutamate-Cysteine Ligase Activity /// Oxidoreductase Activity /// Ligase Activity	---
202615_at	GNAQ	Guanine Nucleotide Binding Protein (G Protein), Q Polypeptide	Protein Amino Acid Adp-Ribosylation /// Signal Transduction /// G-Protein Coupled Receptor Protein Signaling Pathway /// Phospholipase C Activation /// Blood Coagulation	Nucleotide Binding /// Gtpase Activity /// Signal Transducer Activity /// Gtp Binding /// Guanyl Nucleotide Binding	Cytoplasm /// Heterotrimeric G-Protein Complex /// Plasma Membrane
220404_at	GPR97	G Protein- Coupled Receptor 97	Signal Transduction /// Neuropeptide Signaling Pathway /// G-Protein Coupled Receptor Protein Signaling Pathway	Receptor Activity /// G-Protein Coupled Receptor Activity /// Signal Transducer Activity	Membrane /// Integral To Membrane /// Integral To Membrane
211630_s_at	GSS	Glutathione Synthetase /// Glutathione Synthetase	Amino Acid Metabolism /// Glutathione Biosynthesis /// Response To Oxidative Stress /// Nervous System Development	Nucleotide Binding /// Glutathione Synthase Activity /// Atp Binding /// Ligase Activity /// Glutathione Synthase Activity	---
204805_s_at	H1FX	H1 Histone Family, Member X	Nucleosome Assembly /// Chromosome Organization And Biogenesis (Sensu Eukaryota) /// Nucleosome Assembly	Dna Binding /// Dna Binding	Nucleosome /// Nucleus /// Chromosome /// Nucleosome
214500_at	H2AFY	H2A Histone Family, Member Y	Nucleosome Assembly /// Chromosome Organization And Biogenesis (Sensu Eukaryota) /// Dosage Compensation /// Nucleosome Assembly	Dna Binding /// Dna Binding	Nucleosome /// Nucleus /// Chromosome /// Barr Body /// Nucleosome

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201007_at	HADHB	Hydroxyacyl-Coenzyme A Dehydrogenase/3-Ketoacyl-Coenzyme A Thiolase/Enoyl-Coenzyme A Hydratase (Trifunctional Protein), Beta Subunit	Lipid Metabolism /// Fatty Acid Metabolism /// Fatty Acid Beta-Oxidation /// Fatty Acid Biosynthesis	3-Hydroxyacyl-CoA Dehydrogenase Activity /// Acetyl-CoA C-Acyltransferase Activity /// Enoyl-CoA Hydratase Activity /// Acyltransferase Activity /// Transferase Activity /// Acetyl-CoA C-Acyltransferase Activity /// Catalytic Activity	Mitochondrial Membrane /// Mitochondrion
217937_s_at	HDAC7A	Histone Deacetylase 7A	Regulation Of Progression Through Cell Cycle /// Transcription /// Regulation Of Transcription, Dna-Dependent /// Inflammatory Response /// Nervous System Development /// Chromatin Modification /// B Cell Differentiation /// Negative Regulation Of Striated Muscle Development /// Chromatin Modification /// B Cell Activation	Histone Deacetylase Activity /// Transcription Factor Binding /// Specific Transcriptional Repressor Activity /// Hydrolase Activity /// Protein Binding	Histone Deacetylase Complex /// Nucleus /// Cytoplasm /// Nucleus
219863_at	HERC5	Hect Domain And Rld 5	Regulation Of Cyclin Dependent Protein Kinase Activity /// Ubiquitin Cycle /// ProteinModification	Ubiquitin-Protein Ligase Activity /// Ligase Activity	Intracellular

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202814_s_at	HEXIM1	Hexamethylene Bis-Acetamide Inducibl1	Negative Regulation Of Transcription From Rna Polymerase Ii Promoter /// Negative Regulation Of Cyclin Dependent Protein Kinase Activity	Protein Binding /// Cyclin-Dependent Protein Kinase Inhibitor Activity /// Transcriptional Repressor Activity /// Snrna Binding	Nucleus /// Cytoplasm
204689_at	HHEX	Hematopoietically Expressed Homeobox	Regulation Of Transcription, Dna- Dependent /// Development /// Antimicrobial Humoral Response (Sensu Vertebrata) /// Development /// Regulation Of Transcription	Transcription Factor Activity /// Dna Binding /// Transcription Factor Activity /// Dna Binding	Nucleus /// Nucleus
1558561_at	HM13	Histocompatibility (Minor) 13	---	Protein Binding /// Peptidase Activity /// D-Alanyl-D- Alanine Endopeptidase Activity /// Hydrolase Activity	Endoplasmic Reticulum /// Integral To Membrane
200014_s_at	HNRPC	Heterogeneous Nuclear Ribonucleoprotein C (C1/C2) /// Heterogeneous Nuclear Ribonucleoprotein C (C1/C2)	Rna Splicing	Nucleotide Binding /// Rna Binding /// Nucleic Acid Binding /// Rna Binding	Heterogeneous Nuclear Ribonucleoprotein Complex /// Nucleus /// Ribonucleoprotein Complex /// Nucleus
214918_at	HNRPM	Heterogeneous Nuclear Ribonucleoprotein M	---	Nucleotide Binding /// Rna Binding /// Transmembrane Receptor Activity /// Nucleic Acid Binding /// Receptor Activity	Membrane Fraction /// Nucleus /// Plasma Membrane /// Integral To Plasma Membrane /// Ribonucleoprotein Complex

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231271_x_at	HSCARG	Hscarg Protein	Regulation Of Nitrogen Utilization	Transcriptional Repressor Activity	---
202581_at	HSPA1B	Heat Shock 70Kda Protein 1B	Mrna Catabolism /// Protein Folding /// Response To Unfolded Protein /// Protein Biosynthesis /// Translational Elongation /// Response To Unfolded Protein	Nucleotide Binding /// Atp Binding /// Unfolded Protein Binding /// Protein Binding /// Translation Elongation Factor Activity /// Gtp Binding	Nucleus /// Cytoplasm /// Cytoplasm
212493_s_at	HYPB	Huntingtin Interacting Protein B	---	---	---
202439_s_at	IDS	Iduronate 2- Sulfatase (Hunter Syndrome)	Metabolism /// Glycosaminoglycan Metabolism	Iduronate-2- Sulfatase Activity /// Sulfuric Ester Hydrolase Activity /// Hydrolase Activity /// Iduronate-2- Sulfatase Activity	Lysosome /// Lysosome
218611_at	IER5	Immediate Early Response 5	---	---	---
202411_at	IFI27	Interferon, Alpha- Inducible Protein 27	Immune Response /// Response To Pest, Pathogen Or Parasite	---	Integral To Membrane /// Integral To Membrane
204439_at	IFI44L	Interferon-Induced Protein 44-Like	---	---	---
203153_at	IFIT1	Interferon-Induced Protein With Tetratricopeptide Repeats 1 /// InterferoInduced Protein With Tetratricopeptide Repeats 1	Immune Response	Binding	Cytoplasm
217502_at	IFIT2	Interferon-Induced Protein With Tetratricopeptide Repeats 2	Immune Response	Binding	---
229450_at	IFIT3	Interferon-Induced Protein With Tetratricopeptide Repeats 3	Immune Response	Binding	---

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203595_s_at	IFIT5	Interferon-Induced Protein With Tetratricopeptide Repeats 5	Immune Response	Binding	---
201642_at	IFNGR2	Interferon Gamma Receptor 2 (Interferon Gamma Transducer 1)	Cell Surface Receptor Linked Signal Transduction /// Response To Virus /// Response To Pathogen/Bacteria	Receptor Activity /// Hematopoietin/Interferon-Class (D200-Domain) Cytokine Receptor Activity /// Interferon-Gamma Receptor Activity	Integral To Plasma Membrane /// Membrane /// Integral To Membrane
203126_at	IMPA2	Inositol(Myo)-1(Or 4)-Monophosphatase 2	Phosphate Metabolism /// Signal Transduction	Magnesium Ion Binding /// Inositol-1(Or 4)-Monophosphatase Activity /// Hydrolase Activity /// Inositol Or Phosphatidylinositol Phosphatase Activity /// Inositol-1(Or 4)-Monophosphatase Activity /// Metal Ion Binding	---
203275_at	IRF2	Interferon Regulatory Factor 2	Negative Regulation Of Transcription From Rna Polymerase Ii Promoter /// Transcription /// Regulation Of Transcription, Dna-Dependent /// Immune Response /// Cell Proliferation	Transcription Factor Activity /// Rna Polymerase Ii Transcription Factor Activity /// Dna Binding	Nucleus

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208436_s_at	IRF7	Interferon Regulatory Factor 7	Negative Regulation Of Transcription From Rna Polymerase Ii Promoter /// Transcription /// Regulation Of Transcription, Dna- Dependent /// Transcription Initiation From Rna Polymerase Ii Promoter /// Inflammatory Response /// Response To Dna Damage Stimulus /// Response To Virus /// Passive Viral Induction Of Host Immune Response /// Viral Induction Of Host Immune Response /// Response To Virus /// Negative Regulation Of Transcription	Transcription Factor Activity /// Specific Rna Polymerase Ii Transcription Factor Activity /// Dna Binding /// Rna Polymerase Ii Transcription Factor Activity /// Dna Binding /// Transcriptional Repressor Activity	Nucleus /// Cytoplasm /// Nucleus /// Nucleus
203882_at	ISGF3G	Interferon- Stimulated Transcription Factor 3, Gamma 48Kda	Transcription /// Regulation Of Transcription, Dna- Dependent /// Transcription From Rna Polymerase Ii Promoter /// Immune Response /// Cell Surface Receptor Linked Signal Transduction /// Response To Virus /// Protein Ubiquitination	Transcription Factor Activity /// Ubiquitin- ProteinLigase Activity /// Zinc Ion Binding /// Metal Ion Binding /// Dna Binding /// Transcription Factor Activity	Ubiquitin Ligase Complex /// Nucleus /// Cytoplasm /// Nucleus
1553530_a_at	ITGB1	Integrin, Beta 1 (Fibronectin Receptor, Beta Polypeptide, Antigen Cd29 Includes Mdf2, Msk12)	Cellular Defense Response /// Cell Adhesion /// Homophilic Cell Adhesion /// Cell- Matrix Adhesion /// Integrin-Mediated Signaling Pathway /// Development	Receptor Activity /// Protein Binding /// Protein Binding /// Protein Heterodimerization Activity /// Protein Self Binding	Integrin Complex /// Integrin Complex /// Integral To Membrane
209907_s_at	ITSN2	Intersectin 2	Endocytosis	Sh3/Sh2 Adaptor Activity /// Calcium Ion Binding /// Protein Binding	---

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223412_at	KBTBD7	Kelch Repeat And Btb (Poz) Domain Containing 7	---	Protein Binding	---
227647_at	KCNE3	Potassium Voltage-Gated Channel, Isk-Related Family, Member 3	Ion Transport /// Potassium Ion Transport /// Transport	Voltage-Gated Potassium Channel Activity /// Potassium Ion Binding /// Ion Channel Activity /// Voltage-Gated Ion Channel Activity	Voltage-Gated Potassium Channel Complex /// Membrane /// Integral To Membrane
200617_at	KIAA0152	Kiaa0152	---	---	Integral To Membrane
226808_at	KIAA0543	Likely Ortholog Of Mouse Sco-Spondin	Regulation Of Transcription, Dna-Dependent /// Cell Adhesion	Nucleic Acid Binding /// Protein Dimerization Activity	Intracellular
229001_at	KIAA1443	Kiaa1443	Regulation Of Transcription, Dna-Dependent	Transcription Factor Activity	Nucleus
233893_s_at	KIAA1530	Kiaa1530 Protein	---	---	---
231956_at	KIAA1618	Kiaa1618	---	Catalytic Activity	---
226720_at	KIAA1935	Kiaa1935 Protein	---	Methyltransferase Activity /// Transferase Activity	---
219371_s_at	KLF2	Kruppel-Like Factor 2 (Lung)	Transcription /// Regulation Of Transcription, Dna-Dependent	Transcription Factor Activity /// Zinc Ion Binding /// Transcriptional Activator Activity /// Metal Ion Binding /// Nucleic Acid Binding /// Dna Binding	Nucleus /// Nucleus
1555832_s_at	KLF6	Kruppel-Like Factor 6	Transcription /// Regulation Of Transcription, Dna-Dependent /// B Cell Differentiation /// Regulation Of Transcription, Dna-Dependent /// Cell Growth	Dna Binding /// Zinc Ion Binding /// Transcriptional Activator Activity /// Metal Ion Binding /// Nucleic Acid Binding	Nucleus /// Nucleus
210313_at	LILRA4	Leukocyte Immunoglobulin-Like Receptor, Subfamily A (With Tm Domain), Member 4	Immune Response	Receptor Activity	Integral To Membrane
215838_at	LILRA5	Leukocyte Immunoglobulin-Like Receptor, Subfamily A (With Tm Domain), Member 5	---	---	---

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200704_at	LITAF	Lipopolysaccharide-Induced Tnf Factor	Transcription /// Regulation Of Transcription From Rna Polymerase Ii Promoter /// Positive Regulation Of I-KappaB Kinase/Nf-KappaB Cascade /// Regulation Of Transcription, Dna-Dependent	Rna Polymerase Ii Transcription Factor Activity /// Signal Transducer Activity	Nucleus
220036_s_at	LMBR1L	Limb Region 1 Homolog (Mouse)-Like	---	Receptor Activity	---
226375_at	LMTK2	Lemur Tyrosine Kinase 2	Protein Amino Acid Phosphorylation /// Protein Amino Acid Autophosphorylation /// Protein Amino Acid Phosphorylation /// Protein Amino Acid Phosphorylation /// Protein Amino Acid Autophosphorylation	Protein Serine/Threonine Kinase Activity /// Protein Phosphatase Inhibitor Activity /// Protein Binding /// Atp Binding /// Nucleotide Binding /// Protein Kinase Activity /// Protein-Tyrosine Kinase Activity /// Atp Binding /// Kinase Activity /// Transferase Activity /// Protein Binding /// Protein Serine/Threonine Kinase Activity /// Protein Phosphatase Inhibitor Activity /// Atp Binding	Integral To Membrane /// Integral To Membrane
226702_at	LOC129607	Hypothetical Protein Loc129607	Dtdp Biosynthesis /// DtdpBiosynthesis	Thymidylate Kinase Activity /// Atp Binding /// Kinase Activity	---
224990_at	LOC201895	Hypothetical Protein Loc201895	---	Protein Binding	---
226640_at	LOC221955	Kccr13L	Lipid Metabolism	Triacylglycerol Lipase Activity	---
225794_s_at	LOC91689	Hypothetical Gene Supported By AI449243	---	---	---
228320_x_at	LOC92558	Hypothetical Protein Loc92558	---	---	---

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204692_at	LRCH4	Leucine-Rich Repeats And Calponin Homology (Ch) Domain Containing 4	Nervous System Development	---	---
223552_at	LRRC4	Leucine Rich Repeat Containing 4	---	---	Integral To Membrane
205859_at	LY86	Lymphocyte Antigen 86	Apoptosis /// Inflammatory Response /// Humoral Immune Response /// Signal Transduction /// Cell Proliferation /// Immune Response	Signal Transducer Activity	Plasma Membrane
226748_at	LYSMD2	Lysm, Putative Peptidoglycan-Binding, Domain Containing 2	Cell Wall Catabolism	---	---
207922_s_at	MAEA	Macrophage Erythroblast Attacher	Apoptosis /// Cell Adhesion /// Development	---	Membrane Fraction /// Integral To Plasma Membrane
204970_s_at	MAFG	V-Maf Musculoaponeurotic Fibrosarcoma Oncogene Homolog G (Avian)	Transcription /// Regulation Of Transcription, Dna-Dependent /// Transcription From Rna Polymerase Ii Promoter	Transcription Factor Activity /// Dna Binding	Chromatin /// Nucleus
228582_x_at	MALAT1	Metastasis Associated Lung Adenocarcinoma Transcript 1 (Non-Coding Rna)	---	---	---
232333_at	MAML2	Mastermind-Like 2 (Drosophila)	Transcription /// Regulation Of Transcription, Dna-Dependent /// Notch Signaling Pathway /// Positive Regulation Of Transcription From Rna Polymerase Ii Promoter /// Notch Signaling Pathway	Transcription Coactivator Activity /// Catalytic Activity /// Protein Binding /// CampResponse Element Binding Protein Binding	Nucleus /// Nucleus

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232726_at	MAML3	Mastermind-Like 3 (Drosophila)	Transcription /// Regulation Of Transcription, Dna-Dependent /// Notch Signaling Pathway /// Positive Regulation Of Transcription From Rna Polymerase Ii Promoter	Transcription Coactivator Activity	Nucleus
208785_s_at	MAP1LC3B	Microtubule- Associated Protein 1 Light Chain 3 Beta	Ubiquitin Cycle /// Autophagy	Protein Binding	Microtubule /// Membrane /// Autophagic Vacuole /// Organelle Membrane /// Vacuole
203837_at	MAP3K5	Mitogen- Activated Protein Kinase Kinase Kinase 5	Mapkkk Cascade /// Protein Amino Acid Phosphorylation /// Apoptosis /// Response To Stress /// Activation Of Jnk Activity /// Induction Of Apoptosis By Extracellular Signals	Nucleotide Binding /// Magnesium Ion Binding /// Protein Serine/Threonine Kinase Activity /// Map Kinase Kinase Kinase Activity /// Protein- Tyrosine Kinase Activity /// Atp Binding /// Transferase Activity /// Protein Self Binding /// Protein Binding /// Protein Kinase Activity /// Kinase Activity /// Metal Ion Binding	---
1552264_a_at	MAPK1	Mitogen- Activated Protein Kinase 1	Protein Amino Acid Phosphorylation /// Induction Of Apoptosis /// Chemotaxis /// Response To Stress /// Cell Cycle /// Signal Transduction /// Synaptic Transmission	Nucleotide Binding /// Protein Serine/Threonine Kinase Activity /// Map Kinase Activity /// Protein-Tyrosine Kinase Activity /// Atp Binding /// Transferase Activity /// Protein Kinase Activity /// Map Kinase Activity /// Kinase Activity	---
211574_s_at	MCP	Membrane Cofactor Protein (Cd46, Trophoblast- Lymphocyte Cross- Reactive Antigen)	Immune Response /// Complement Activation, Classical Pathway /// Innate Immune Response /// Complement Activation	Receptor Activity	Plasma Membrane /// Integral To Plasma Membrane /// Integral To Membrane

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225742_at	MDM4	Mdm4, Transformed 3T3 Cell Double Minute 4, P53 Binding Protein (Mouse)	Negative Regulation Of Transcription From Rna Polymerase Ii Promoter /// Protein Complex Assembly /// Apoptosis /// Cell Proliferation /// Negative Regulation Of Cell Proliferation /// Protein Ubiquitination /// Negative Regulation Of Protein Catabolism /// G0 To G1 Transition /// Protein Stabilization	Ubiquitin-Protein Ligase Activity /// Protein Binding /// Zinc Ion Binding /// Metal Ion Binding /// Zinc Ion Binding	Ubiquitin Ligase Complex /// Nucleus /// Nucleus
223264_at	MESDC1	Mesoderm Development Candidate 1	---	---	---
206522_at	MGAM	Maltase- Glucoamylase (Alpha- Glucosidase)	Carbohydrate Metabolism /// Starch Catabolism	Glucan 1,4-Alpha- Glucosidase Activity /// Hydrolase Activity, Hydrolyzing O- Glycosyl Compounds /// Alpha-Glucosidase Activity /// Catalytic Activity /// Hydrolase Activity /// Hydrolase Activity, Acting On Glycosyl Bonds /// Catalytic Activity	Integral To Membrane
225568_at	MGC14141	Hypothetical Protein Mgc14141	---	---	---
221756_at	MGC17330	Hgfl Gene /// Hgfl Gene	---	---	---
244716_x_at	MGC23244	Hypothetical Protein Mgc23244	---	---	---

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225995_x_at	MGC52000	Cxyorf1-Related Protein	---	---	---
201298_s_at	MOBK1B	Mob1, Mps One Binder Kinase ActivatorLike 1B (Yeast)	----	Metal Ion Binding /// Zinc Ion Binding	---
222555_s_at	MRPL44	Mitochondrial Ribosomal Protein L44	Rna Processing	Double-Stranded Rna Binding /// Structural Constituent Of Ribosome /// Endonuclease Activity /// Ribonuclease Iii Activity /// Hydrolase Activity /// Rna Binding /// Nuclease Activity	Mitochondrion /// Ribonucleoprotein Complex /// Intracellular
232724_at	MS4A6A	Membrane-Spanning 4-Domains, Subfamily A, Member 6A	Signal Transduction	Receptor Activity	Integral To Membrane
218773_s_at	MSRB2	Methionine Sulfoxide Reductase B2	Protein Repair	Protein-Methionine-R-Oxide Reductase Activity /// Transcription Factor Activity /// Zinc Ion Binding /// Oxidoreductase Activity	Mitochondrion
216336_x_at	MT1K	Metallothionein 1M	---	Copper Ion Binding /// Cadmium Ion Binding /// Metal Ion Binding	---
202086_at	MX1	Myxovirus (Influenza Virus) Resistance 1, Interferon-Inducible Protein P78 (Mouse) /// Myxovirus (Influenza Virus) Resistance 1, Interferon-Inducible Protein P78 (Mouse)	Induction Of Apoptosis /// Immune Response /// Signal Transduction /// Response To Virus /// Defense Response	Nucleotide Binding /// Gtpase Activity /// Gtp Binding /// Gtp Binding /// Gtpase Activity	Cytoplasm

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204994_at	MX2	Myxovirus (Influenza Virus) Resistance 2 (Mouse)	Immune Response /// Response To Virus /// Defense Response	Nucleotide Binding /// Gtpase Activity /// Gtp Binding /// Gtpase Activity	Nucleus /// Cytoplasm
203360_s_at	MYCBP	C-Myc Binding Protein	Transcription /// Regulation Of Transcription, Dna- Dependent	Transcription Coactivator Activity /// Protein Binding	Nucleus /// Mitochondrion /// Cytoplasm /// Nucleus /// Cytoplasm
220319_s_at	MYLIP	Myosin Regulatory Light Chain Interacting Protein	Cell Motility /// Nervous System Development /// Protein Ubiquitination /// Ubiquitin Cycle /// ProteinUbiquitination	Ubiquitin-Protein Ligase Activity /// Cytoskeletal Protein Binding /// Zinc Ion Binding /// Ligase Activity /// Metal Ion Binding /// Protein Binding /// Ubiquitin- Protein Ligase Activity /// Binding /// Cytoskeletal Protein Binding	Ubiquitin Ligase Complex /// Cytoplasm /// Cytoskeleton /// Membrane /// Intracellular
1567013_at	NFE2L2	Nuclear Factor (Erythroid- Derived 2)- Like 2	Transcription /// Regulation Of Transcription, Dna- Dependent /// Transcription From Rna Polymerase Ii Promoter	Transcription Factor Activity /// Dna Binding /// Serine- Type Endopeptidase Inhibitor Activity	Nucleus
203574_at	NFIL3	Nuclear Factor, Interleukin 3 Regulated	Regulation Of Transcription, Dna- Dependent /// Transcription From Rna Polymerase Ii Promoter /// Immune Response	Dna Binding /// Dna Binding /// Transcription Factor Activity /// Transcription Corepressor Activity	Nucleus /// Nucleus
217830_s_at	NSFL1C	Nsfl1 (P97) Cofactor (P47)	---	Lipid Binding	Nucleus /// Golgi Stack
222424_s_at	NUCKS1	Nuclear Casein Kinase And Cyclin- Dependent Kinase Substrate 1	---	Kinase Activity	Nucleus

Affymetrix probeset ID	Gene Symbol	Gene Description	GO Biological Process	GO Molecular Function	GO Cellular Component
211973_at	NUDT3	Nudix (Nucleoside Diphosphate Linked Moiety X)- Type Motif 3	Intracellular Signaling Cascade /// Cell- Cell Signaling /// Diadenosine Polyphosphate Catabolism /// Calcium- Mediated Signaling /// Cyclic- Nucleotide- Mediated Signaling /// Regulation Of Rna Export From Nucleus /// Intracellular Transport	Magnesium Ion Binding /// Diphosphoinositol- Polyphosphate Diphosphatase Activity /// Hydrolase Activity /// Diphosphoinositol- Polyphosphate Diphosphatase Activity /// Metal Ion Binding /// Diphosphoinositol- Polyphosphate Diphosphatase Activity	Intracellular
204972_at	OAS2	2'-5'- Oligoadenylate Synthetase 2, 69/71Kda	Nucleobase, Nucleoside, Nucleotide And Nucleic Acid Metabolism /// Immune Response	Rna Binding /// Atp Binding/// Transferase Activity /// Nucleotidyltransferase Activity /// Nucleic Acid Binding	Microsome /// Membrane
218400_at	OAS3	2'-5'- Oligoadenylate Synthetase 3, 100Kda	Nucleobase, Nucleoside, Nucleotide And Nucleic Acid Metabolism /// Immune Response	Rna Binding /// Atp Binding/// Transferase Activity /// Nucleotidyltransferase Activity /// Nucleic Acid Binding	Microsome
205660_at	OASL	2'-5'- Oligoadenylate Synthetase-Like	Protein Modification /// Immune Response	Dna Binding /// Double- Stranded Rna Binding /// Atp Binding /// Transferase Activity /// Thyroid Hormone Receptor Binding /// Nucleic Acid Binding /// Rna Binding	Nucleolus /// Cytoplasm
201599_at	OAT	Ornithine Aminotransferase (Gyrate Atrophy)	Amino Acid Metabolism /// Ornithine Metabolism /// Visual Perception	Ornithine-Oxo-Acid Transaminase Activity /// Transferase Activity /// Pyridoxal Phosphate Binding /// Ornithine- Oxo-Acid Transaminase Activity /// Transaminase Activity	Mitochondrial Matrix /// Mitochondrion /// Mitochondrion

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205760_s_at	OGG1	8-Oxoguanine Dna Glycosylase	Carbohydrate Metabolism /// Base-Excision Repair /// Dna Repair /// Base- Excision Repair /// Response To Dna Damage Stimulus /// Dna Repair	Damaged Dna Binding /// Endonuclease Activity /// Purine-Specific Oxidized Base Lesion Dna N- Glycosylase Activity /// Hydrolase Activity, Acting On Glycosyl Bonds /// Lyase Activity /// Dna Binding /// Catalytic Activity /// Dna-(Apurinic Or Apyrimidinic Site) Lyase Activity /// Purine- Specific Oxidized Base Lesion Dna N-Glycosylase Activity /// Hydrolase Activity /// Purine-Specific Oxidized Base Lesion Dna N-Glycosylase Activity	Nucleoplasm /// Mitochondrion /// Nucleus
207091_at	P2RX7	Purinergic Receptor P2X, Ligand-Gated Ion Channel, 7	Ion Transport /// Signal Transduction /// Transport /// Transport	Receptor Activity /// Atp- Gated Cation Channel Activity /// Ion Channel Activity /// Atp Binding /// Receptor Activity	Integral To Plasma Membrane /// Membrane /// Integral To Membrane
218809_at	PANK2	Pantothenate Kinase 2 (Hallervorden- Spatz Syndrome)	Coenzyme A Biosynthesis	Nucleotide Binding /// Pantothenate Kinase Activity /// Atp Binding /// Transferase Activity /// Kinase Activity	---
223220_s_at	PARP9	Poly (Adp- Ribose) Polymerase Family, Member 9	Protein Amino Acid Adp- Ribosylation /// Cell Migration	Nad+ Adp- Ribosyltransferase Activity	Nucleus /// Nucleus

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203708_at	PDE4B	Phosphodiesterase 4B, Camp-Specific (Phosphodiesterase E4 Duncce Homolog, Drosophila)	Signal Transduction	Camp-Specific Phosphodiesterase Activity /// Hydrolase Activity /// Catalytic Activity /// 3',5'-Cyclic-Nucleotide Phosphodiesterase Activity	Soluble Fraction /// Insoluble Fraction
207668_x_at	PDIA6	Protein Disulfide Isomerase Family A, Member 6	Electron Transport /// Protein Folding	Protein Disulfide Isomerase Activity /// Electron Transporter Activity /// Isomerase Activity /// Protein Disulfide Isomerase Activity	Endoplasmic Reticulum
202464_s_at	PFKFB3	6-Phosphofructo-2-Kinase/Fructose-2,6-Biphosphatase 3	Fructose 2,6-Bisphosphate Metabolism /// Fructose 2,6-Bisphosphate Metabolism /// Metabolism	Nucleotide Binding /// Catalytic Activity /// 6-Phosphofructo-2-Kinase Activity /// Fructose-2,6-Bisphosphate 2-Phosphatase Activity /// Atp Binding /// Kinase Activity /// Transferase Activity /// Hydrolase Activity /// 6-Phosphofructo2-Kinase Activity	---
218517_at	PHF17	Phd Finger Protein 17	Regulation Of Transcription, Dna-Dependent /// Apoptosis /// Response To Stress /// Negative Regulation Of Cell Growth /// Apoptosis /// Response To Stress /// Negative Regulation Of Cell Growth	Protein Binding /// Zinc Ion Binding /// Protein Binding /// Protein Binding	Nucleus /// Cytoplasm /// Nucleus /// Cytoplasm
203278_s_at	PHF21A	Phd Finger Protein 21A	Regulation Of Transcription, Dna-Dependent /// Transcription	Protein Binding /// Zinc Ion Binding /// Dna Binding /// Helicase Activity /// Metal Ion Binding	---

<i>Affymetrix probeset ID</i>	<i>Gene Symbol</i>	<i>Gene Description</i>	<i>GO Biological Process</i>	<i>GO Molecular Function</i>	<i>GO Cellular Component</i>
203691_at	PI3	Peptidase Inhibitor 3, Skin-Derived (Skalp) /// Peptidase Inhibitor 3, Skin-Derived (Skalp)	Copulation	Serine-Type Endopeptidase Inhibitor Activity /// Protein Binding /// Endopeptidase Inhibitor Activity /// Serine-Type Endopeptidase Inhibitor Activity /// Endopeptidase Inhibitor Activity	Extracellular Matrix (Sensu Metazoa) /// Extracellular Region
210845_s_at	PLAUR	Plasminogen Activator, Urokinase Receptor	Cell Motility /// Chemotaxis /// Cell Surface Receptor Linked Signal Transduction /// Blood Coagulation /// Regulation Of Proteolysis /// Signal Transduction /// Blood Coagulation	Protein Binding /// U- Plasminogen Activator Receptor Activity /// Receptor Activity /// U- Plasminogen Activator Receptor Activity /// Receptor Activity /// Receptor Activity /// Kinase Activity	Plasma Membrane /// Cell Surface /// Integral To Membrane /// Extrinsic To Membrane /// Membrane
202430_s_at	PLSCR1	Phospholipid Scramblase 1	Response To Virus /// Phospholipid Scrambling /// Platelet Activation	Calcium Ion Binding /// Phospholipid Scramblase Activity /// Calcium Ion Binding	Plasma Membrane /// Integral To Membrane

<i>Affymetrix probeset ID</i>	<i>Gene Symbol</i>	<i>Gene Description</i>	<i>GO Biological Process</i>	<i>GO Molecular Function</i>	<i>GO Cellular Component</i>
200695_at	PPP2R1A	Protein Phosphatase 2 (Formerly 2A), Regulatory Subunit A (Pr 65), Alpha Isoform	Regulation Of Progression Through Cell Cycle /// Inactivation Of Mapk Activity /// Regulation Of Dna Replication /// Regulation Of Translation /// Protein Complex Assembly /// Protein Amino Acid Dephosphorylation /// Ceramide Metabolism /// Induction Of Apoptosis /// Rna Splicing /// Response To Organic Substance /// Second-Messenger-Mediated Signaling /// Regulation Of Wnt Receptor Signaling Pathway /// Regulation Of Cell Adhesion /// Negative Regulation Of Cell Growth /// Regulation Of Growth /// Negative Regulation Of Tyrosine Phosphorylation Of Stat3 Protein /// Regulation Of Transcription /// Regulation Of Cell Differentiation	Antigen Binding /// Phosphoprotein Phosphatase Activity /// Protein Binding /// Protein Phosphatase Type 2A Regulator Activity /// Hydrolase Activity /// Protein Heterodimerization Activity /// Binding	Protein Phosphatase Type 2A Complex /// Soluble Fraction /// Nucleus /// Mitochondrion /// Cytosol /// Microtubule Cytoskeleton /// Membrane
201859_at	PRG1	Proteoglycan 1, Secretory Granule	---	---	---
201762_s_at	PSME2	Proteasome (Prosome, Macropain) Activator Subunit 2 (Pa28 Beta)	Immune Response	Proteasome Activator Activity	Proteasome Complex (Sensu Eukaryota) /// Proteasome Activator Complex /// Cytosol /// Protein Complex

<i>Affymetrix probeset ID</i>	<i>Gene Symbol</i>	<i>Gene Description</i>	<i>GO Biological Process</i>	<i>GO Molecular Function</i>	<i>GO Cellular Component</i>
201433_s_at	PTDSS1	Phosphatidylserine Synthase 1	Phosphatidylserine Biosynthesis /// Phospholipid Biosynthesis	Transferase Activity	Integral To Membrane
200730_s_at	PTP4A1	Protein Tyrosine Phosphatase Type Iva, Member 1	Protein Amino Acid Dephosphorylation /// Cell Cycle /// Development	Protein Tyrosine Phosphatase Activity /// Hydrolase Activity /// Phosphoprotein Phosphatase Activity	Endoplasmic Reticulum /// Membrane
208616_s_at	PTP4A2	Protein Tyrosine Phosphatase Type Iva, Member 2	Protein Amino Acid Dephosphorylation	Prenylated Protein Tyrosine Phosphatase Activity /// Hydrolase Activity /// Phosphoprotein Phosphatase Activity /// Protein Tyrosine Phosphatase Activity	Membrane
205174_s_at	QPCT	Glutaminyl-Peptide Cyclotransferase (Glutaminyl Cyclase)	Protein Modification /// Proteolysis	Peptidase Activity /// Acyltransferase Activity /// Glutaminyl-Peptide Cyclotransferase Activity /// Transferase Activity	---
209514_s_at	RAB27A	Rab27A, Member Ras Oncogene Family	Intracellular Protein Transport /// Small Gtpase Mediated Signal Transduction /// Protein Transport	Nucleotide Binding /// Gtpase Activity /// Gtp Binding	---
221808_at	RAB9A	Rab9A, Member Ras Oncogene Family	Intracellular Protein Transport /// Small Gtpase Mediated Signal Transduction /// Transport /// Protein Transport	Nucleotide Binding /// Gtpase Activity /// Gtp Binding	Golgi Stack /// Lysosome /// Late Endosome
202100_at	RALB	V-Ral Simian Leukemia Viral Oncogene Homolog B (Ras Related; Gtp Binding Protein)	Intracellular Protein Transport /// Signal Transduction /// Small Gtpase Mediated Signal Transduction	Nucleotide Binding /// Gtp Binding /// Gtp Binding	---

<i>Affymetrix probeset ID</i>	<i>Gene Symbol</i>	<i>Gene Description</i>	<i>GO Biological Process</i>	<i>GO Molecular Function</i>	<i>GO Cellular Component</i>
244674_at	RBM6	Rna Binding Motif Protein 6	Rna Processing	Nucleotide Binding /// Dna Binding /// Rna Binding /// Nucleic Acid Binding /// Rna Binding	Nucleus /// Intracellular /// Nucleus
217775_s_at	RDH11	Retinol Dehydrogenase 11 (All-Trans And 9-Cis)	Metabolism /// Retinol Metabolism /// Photoreceptor Maintenance /// Visual Perception	Retinol Dehydrogenase Activity /// Oxidoreductase Activity	Intracellular /// Endoplasmic Reticulum /// Integral To Membrane
229285_at	RNASEL	Ribonuclease L (2',5'-Oligoisoadenylate Synthetase-Dependent)	Mrna Processing /// Protein Amino Acid Phosphorylation /// Protein Amino Acid Phosphorylation	Rna Binding /// Protein Serine/Threonine Kinase Activity /// Atp Binding /// Hydrolase Activity /// Endoribonuclease Activity, Producing 5'-Phosphomonoesters /// Metal Ion Binding /// Nucleotide Binding /// Protein Kinase Activity /// Kinase Activity /// Transferase Activity	---
225414_at	RNF149	Ring Finger Protein 149	Proteolysis /// Protein Ubiquitination	Ubiquitin-Protein Ligase Activity /// Peptidase Activity /// Zinc Ion Binding	Ubiquitin Ligase Complex
224947_at	RNF26	Ring Finger Protein 26	Protein Ubiquitination	Ubiquitin-Protein Ligase Activity /// Zinc Ion Binding /// Metal Ion Binding /// Zinc Ion Binding	Ubiquitin Ligase Complex /// Nucleus
219035_s_at	RNF34	Ring Finger Protein 34	Apoptosis /// Protein Ubiquitination /// Ubiquitin Cycle	Ubiquitin-Protein Ligase Activity /// Zinc Ion Binding /// Metal Ion Binding	Ubiquitin Ligase Complex /// Nucleus /// Membrane
211976_at	RPL35	Ribosomal Protein L35	Protein Biosynthesis /// Protein Biosynthesis	Mrna Binding /// Structural Constituent Of Ribosome /// Structural Constituent Of Ribosome	Nucleolus /// Ribosome /// Cytosolic Large Ribosomal Subunit (Sensu Eukaryota) /// Intracellular /// Ribonucleoprotein Complex

<i>Affymetrix probeset ID</i>	<i>Gene Symbol</i>	<i>Gene Description</i>	<i>GO Biological Process</i>	<i>GO Molecular Function</i>	<i>GO Cellular Component</i>
213797_at	RSAD2	Radical S-Adenosyl Methionine Domain Containing 2	---	Catalytic Activity /// Iron Ion Binding	---
210968_s_at	RTN4	Reticulon 4	Negative Regulation Of Anti-Apoptosis /// Negative Regulation Of Axon Extension /// Regulation Of Apoptosis /// Apoptosis	Protein Binding	Nuclear Membrane /// Endoplasmic Reticulum /// Integral To Membrane /// Integral To Endoplasmic Reticulum Membrane /// Endoplasmic Reticulum
222986_s_at	SCOTIN	Scotin	Positive Regulation Of I-Kappab Kinase/Nf-Kappab Cascade	Signal Transducer Activity	Nucleus
202228_s_at	SDFR1	Stromal Cell Derived Factor Receptor 1	---	Receptor Activity	Membrane
209206_at	SEC22L1	Sec22 Vesicle Trafficking Protein-Like 1 (S. Cerevisiae)	Er To Golgi Transport /// Protein Transport /// Vesicle-Mediated Transport /// Transport /// Er To Golgi Transport	---	Endoplasmic Reticulum Membrane /// Golgi Stack /// Integral To Membrane /// Endoplasmic Reticulum
201582_at	SEC23B	Sec23 Homolog B (S. Cerevisiae)	Intracellular Protein Transport /// Er To Golgi Transport /// Vesicle-Mediated Transport /// Transport /// Protein Transport	Protein Binding	Endoplasmic Reticulum /// Golgi Stack /// Membrane /// Copii Vesicle Coat

<i>Affymetrix probeset ID</i>	<i>Gene Symbol</i>	<i>Gene Description</i>	<i>GO Biological Process</i>	<i>GO Molecular Function</i>	<i>GO Cellular Component</i>
212268_at	SERPINB1	Serpin Peptidase Inhibitor, Clade B (Ovalbumin), Member 1	---	Serine-Type Endopeptidase Inhibitor Activity /// Endopeptidase Inhibitor Activity /// Serine-Type Endopeptidase Inhibitor Activity	Cytoplasm
208313_s_at	SF1	Splicing Factor 1	Spliceosome Assembly /// Transcription /// Regulation Of Transcription, Dna- Dependent /// Nuclear Mrna Splicing, Via Spliceosome /// Mrna Processing	Rna Polymerase Ii Transcription Factor Activity /// Transcription Corepressor Activity /// Rna Binding /// Metal Ion Binding /// Nucleic Acid Binding /// Rna Binding /// Zinc Ion Binding /// Nucleic Acid Binding /// Metal Ion Binding	Spliceosome Complex /// Ribosome /// Nucleus /// Nucleus
225056_at	SIPA1L2	Signal-Induced Proliferation-Associated 1 Like 2	---	Gtpase Activator Activity /// Protein Binding	---
203761_at	SLA	Src-Like-Adaptor /// Src- Like-Adaptor	Intracellular Signaling Cascade	Sh3/Sh2 Adaptor Activity	--
205896_at	SLC22A4	Solute Carrier Family 22 (Organic Cation Transporter), Member 4	Ion Transport /// Sodium Ion Transport /// Fluid Secretion /// Organic Cation Transport /// Transport	Nucleotide Binding /// Atp Binding /// Organic Cation Porter Activity /// Ion Transporter Activity /// Symporter Activity /// Sodium Ion Binding /// Nucleotide Binding /// Transporter Activity	Plasma Membrane /// Integral To Plasma Membrane /// Membrane /// Integral To Membrane
218749_s_at	SLC24A6	Solute Carrier Family 24 (Sodium/Potassium/Calcium Exchanger), Member 6	---	---	Integral To Membrane

<i>Affymetrix probeset ID</i>	<i>Gene Symbol</i>	<i>Gene Description</i>	<i>GO Biological Process</i>	<i>GO Molecular Function</i>	<i>GO Cellular Component</i>
202497_x_at	SLC2A3	Solute Carrier Family 2 (Facilitated Glucose Transporter), Member 3	Carbohydrate Metabolism /// Carbohydrate Transport /// Glucose Transport /// Development /// Spermatogenesis /// Cell Differentiation	Transporter Activity /// Sugar Porter Activity /// Glucose Transporter Activity /// Glucose Transporter Activity	Membrane Fraction /// Membrane /// Integral To Membrane /// Integral To Membrane
235013_at	SLC31A1	Solute Carrier Family 31 (Copper Transporters), Member 1	Ion Transport /// Copper Ion Transport /// Copper Ion Transport /// Transport	Copper Ion Transporter Activity /// Copper Ion Transporter Activity /// Copper Ion Binding	Integral To Plasma Membrane /// Integral To Membrane
225175_s_at	SLC44A2	Solute Carrier Family 44, Member 2	Transport /// Positive Regulation Of I-KappaB Kinase/NF-KappaB Cascade	Signal Transducer Activity	Integral To Membrane
209131_s_at	SNAP23	Synaptosomal-Associated Protein, 23Kda	Transport /// Protein Transport /// Post-Golgi Transport /// Vesicle Targeting /// Membrane Fusion	T-Snare Activity	Membrane /// Synaptosome /// Plasma Membrane
208821_at	SNRPB	Small Nuclear Ribonucleoprotein Polypeptides B And B1	Mrna Processing /// Rna Splicing /// Nuclear Mrna Splicing, Via Spliceosome	Rna Binding /// Protein Binding	Spliceosome Complex /// Small Nucleolar Ribonucleoprotein Complex /// Small Nuclear Ribonucleoprotein Complex /// Nucleus /// Ribonucleoprotein Complex /// Small Nucleolar Ribonucleoprotein Complex
221561_at	SOAT1	Sterol O-Acyltransferase (Acyl-Coenzyme A: Cholesterol Acyltransferase) 1	Lipid Metabolism /// Circulation /// Steroid Metabolism /// Cholesterol Metabolism /// Cholesterol Metabolism	Sterol O-Acyltransferase Activity /// Acyltransferase Activity /// Acyltransferase Activity /// Transferase Activity	Endoplasmic Reticulum /// Membrane /// Integral To Membrane /// Endoplasmic Reticulum
208012_x_at	SP110	Sp110 Nuclear Body Protein	Transcription /// Regulation Of Transcription, Dna-Dependent /// Electron Transport	Dna Binding /// Hematopoietin/Interferon-Class (D200-Domain) Cytokine Receptor Signal Transducer Activity /// Protein Binding /// Zinc Ion Binding /// Metal Ion Binding /// Dna Binding /// Electron Transporter Activity	Nucleus /// Nucleus

<i>Affymetrix probeset ID</i>	<i>Gene Symbol</i>	<i>Gene Description</i>	<i>GO Biological Process</i>	<i>GO Molecular Function</i>	<i>GO Cellular Component</i>
221769_at	SPSB3	Spla/Ryanodine Receptor Domain And Socs Box Containing 3	Intracellular Signaling Cascade	---	---
217995_at	SQRDL	Sulfide Quinone Reductase-Like (Yeast)	---	Oxidoreductase Activity	Mitochondrion
201247_at	SREBF2	Sterol Regulatory Element Binding Transcription Factor 2	Regulation Of Transcription From Rna Polymerase Ii Promoter /// Lipid Metabolism /// Steroid Metabolism /// Cholesterol Metabolism /// Transcription /// Regulation Of Transcription, Dna-Dependent /// Lipid Metabolism /// Regulation Of Transcription	Dna Binding /// Rna Polymerase Ii Transcription Factor Activity /// Protein Binding /// Transcription Regulator Activity	Nucleus /// Endoplasmic Reticulum /// Golgi Stack /// Integral To Membrane
208921_s_at	SRI	Sorcin	Regulation Of Action Potential /// Transport /// Intracellular Sequestering Of Iron Ion /// Regulation Of Striated Muscle Contraction /// Heart Development /// Muscle Development /// Regulation Of Heart Contraction Rate	Receptor Binding /// Calcium Channel Regulator Activity /// Calcium Ion Binding	Cytoplasm
210190_at	STX11	Syntaxin 11	Intracellular Protein Transport /// Membrane Fusion /// Transport /// Protein Transport	Snap Receptor Activity /// Protein Transporter Activity	Golgi Stack /// Membrane

<i>Affymetrix probeset ID</i>	<i>Gene Symbol</i>	<i>Gene Description</i>	<i>GO Biological Process</i>	<i>GO Molecular Function</i>	<i>GO Cellular Component</i>
208831_x_at	SUPT6H	Suppressor Of Ty 6 Homolog (S. Cerevisiae)	Nucleobase, Nucleoside, Nucleotide And Nucleic Acid Metabolism /// Chromatin Remodeling /// Regulation Of Transcription, Dna- Dependent /// Intracellular Signaling Cascade /// Transcription /// Regulation Of Transcription, Dna- Dependent	Transcription Factor Activity /// Rna Binding /// Hydrolase Activity, Acting On Ester Bonds	Nucleus /// Nucleus
229723_at	TAGAP	T-Cell Activation Gtpase Activating Protein	---	Guanyl-Nucleotide Exchange Factor Activity	---
202307_s_at	TAP1	Transporter 1, Atp-Binding Cassette, Sub- Family B (Mdr/Tap)	Transport /// Oligopeptide Transport /// Immune Response /// Protein Transport /// Peptide Transport	Nucleotide Binding /// Transporter Activity /// Atp Binding /// Oligopeptide Transporter Activity /// ATPase Activity /// ATPase Activity, Coupled To Transmembrane Movement Of Substances /// Protein Heterodimerization Activity /// Nucleoside- Triphosphatase Activity	Endoplasmic Reticulum /// Integral To Membrane /// Integral To Membrane

<i>Affymetrix probeset ID</i>	<i>Gene Symbol</i>	<i>Gene Description</i>	<i>GO Biological Process</i>	<i>GO Molecular Function</i>	<i>GO Cellular Component</i>
201174_s_at	TERF2IP	Telomeric Repeat Binding Factor 2, Interacting Protein	Telomerase-Dependent Telomere Maintenance /// Regulation Of Transcription /// Telomere Maintenance /// Transcription /// Regulation Of Transcription, Dna-Dependent	Telomeric Dna Binding /// Dna Binding /// Receptor Activity	Nuclear Chromosome /// Chromosome, Telomeric Region /// Nucleus /// Chromosome
205016_at	TGFA	Transforming Growth Factor, Alpha	Regulation Of Progression Through Cell Cycle /// Cell-Cell Signaling /// Cell Proliferation /// Cell Proliferation	Protein-Tyrosine Kinase Activity /// Signal Transducer Activity /// Epidermal Growth Factor Receptor Activating Ligand Activity /// Protein Binding /// Growth Factor Activity	Extracellular Space /// Soluble Fraction /// Plasma Membrane /// Integral To Plasma Membrane /// Integral To Membrane
230651_at	THOC2	Tho Complex 2	Nuclear Mrna Splicing, Via Spliceosome /// Mrna Export From Nucleus /// Transport /// Mrna Processing	Rna Binding	Nucleus
242617_at	TMED8	Transmembrane Emp24 Protein Transport Domain Containing 8	Intracellular Protein Transport	Protein Carrier Activity	Membrane
217795_s_at	TMEM43	Transmembrane Protein 43	---	---	Integral To Membrane
200620_at	TMEM59	Transmembrane Protein 59	---	---	Integral To Membrane
203839_s_at	TNK2	Tyrosine Kinase, Non-Receptor, 2	Protein Amino Acid Phosphorylation /// Cytoskeleton Organization And Biogenesis /// Small Gtpase Mediated Signal Transduction	Nucleotide Binding /// Protein Serine/Threonine Kinase Activity /// Non-Membrane Spanning Protein Tyrosine Kinase Activity /// Gtpase Inhibitor Activity /// Protein Binding /// Atp Binding /// Transferase Activity /// Protein Kinase Activity /// Protein-Tyrosine Kinase Activity /// Kinase Activity	Cytoplasm

<i>Affymetrix probeset ID</i>	<i>Gene Symbol</i>	<i>Gene Description</i>	<i>GO Biological Process</i>	<i>GO Molecular Function</i>	<i>GO Cellular Component</i>
221507_at	TNPO2	Transportin 2 (Importin 3, Karyopherin Beta 2B)	Protein Import Into Nucleus, Docking /// Protein Transport /// Transport	Binding /// Nuclear Localization Sequence Binding /// Protein Transporter Activity	Nucleus /// Nuclear Pore /// Cytoplasm /// Nucleus /// Cytoplasm
237895_at	TNRC6B	Trinucleotide Repeat Containing 6B	Intracellular Protein Transport /// Small Gtpase Mediated Signal Transduction /// Protein Transport	Nucleotide Binding /// Gtp Binding	---
217914_at	TPCN1	Two Pore Segment Channel 1	Transport /// Ion Transport /// Cation Transport	Ion Channel Activity /// Cation Channel Activity /// Calcium Ion Binding	Membrane /// Integral To Membrane
221571_at	TRAF3	Tnf Receptor- Associated Factor 3	Induction Of Apoptosis /// Signal Transduction /// Protein Ubiquitination /// Regulation Of Apoptosis /// Apoptosis /// Signal Transduction	Ubiquitin-Protein Ligase Activity /// Signal Transducer Activity /// Protein Binding /// Zinc Ion Binding /// Metal Ion Binding /// Receptor Activity	Ubiquitin Ligase Complex
216749_at	TRERF1	Transcriptional Regulating Factor 1	Steroid Biosynthesis /// Cholesterol Catabolism /// Development /// Homeostasis /// Regulation Of Transcription /// Positive Regulation Of Transcription, Dna-Dependent /// Regulation Of Hormone Biosynthesis	Transcription Factor Activity /// Transcription Factor Binding /// Zinc Ion Binding /// Dna Bending Activity /// Rna Polymerase Ii Transcription Mediator Activity /// Ligand- Dependent Nuclear Receptor Transcription Coactivator Activity /// Metal Ion Binding /// Nucleic Acid Binding /// Dna Binding	Nucleus /// Nucleus
203148_s_at	TRIM14	Tripartite Motif- Containing 14	Compartment Specification	Protein Binding /// Zinc Ion Binding /// Metal Ion Binding	Cytoplasm /// Intracellular
210705_s_at	TRIM5	Tripartite Motif- Containing 5	Protein Ubiquitination /// Ubiquitin Cycle	Ubiquitin-Protein Ligase Activity /// Zinc Ion Binding /// Ligase Activity /// Metal Ion Binding	Ubiquitin Ligase Complex /// Intracellular

<i>Affymetrix probeset ID</i>	<i>Gene Symbol</i>	<i>Gene Description</i>	<i>GO Biological Process</i>	<i>GO Molecular Function</i>	<i>GO Cellular Component</i>
220558_x_at	TSPAN32	Tetraspanin 32	Cell-Cell Signaling	---	Integral To Membrane /// Integral To Membrane
1557073_s_at	TTBK2	Tau Tubulin Kinase 2	Protein Amino Acid Phosphorylation	Nucleotide Binding /// Protein Kinase Activity /// Atp Binding /// Kinase Activity /// Transferase Activity /// Structural Molecule Activity	Intermediate Filament
202335_s_at	UBE2B	Ubiquitin- Conjugating Enzyme E2B (Rad6 Homolog)	Dna Repair /// Ubiquitin Cycle /// Protein Modification /// ResponseTo Dna Damage Stimulus	Ubiquitin-Protein Ligase Activity /// Ubiquitin-Like Activating Enzyme Activity /// Ligase Activity	Nucleus /// Membrane
200668_s_at	UBE2D3	Ubiquitin- Conjugating Enzyme E2D 3 (Ubc4/5 Homolog, Yeast)	Ubiquitin Cycle /// ProteinModification	Ubiquitin-Protein Ligase Activity /// Protein Binding /// Ubiquitin-Like Activating Enzyme Activity /// Ligase Activity	---
215737_x_at	USF2	Upstream Transcription Factor 2, C-Fos Interacting	Regulation Of Transcription, Dna- Dependent /// Transcription /// Regulation Of Transcription	Transcription Factor Activity /// Rna Polymerase li Transcription Factor Activity /// Dna Binding /// Transcription Regulator Activity	Nucleus
201557_at	VAMP2	Vesicle- Associated Membrane Protein 2 (Synaptobrevin 2)	Vesicle-Mediated Transport	---	Integral To Membrane /// Synaptosome /// Synapse

<i>Affymetrix probeset ID</i>	<i>Gene Symbol</i>	<i>Gene Description</i>	<i>GO Biological Process</i>	<i>GO Molecular Function</i>	<i>GO Cellular Component</i>
204254_s_at	VDR	Vitamin D (1,25-Dihydroxyvitamin D3) Receptor	Transcription /// Regulation Of Transcription, Dna- Dependent /// Signal Transduction /// Negative Regulation Of Transcription	Transcription Factor Activity /// Steroid Hormone Receptor Activity /// Protein Binding /// Vitamin D3 Receptor Activity /// Metal Ion Binding /// Dna Binding /// Protein Binding /// Dna Binding /// Receptor Activity /// Ligand-Dependent Nuclear Receptor Activity /// Zinc Ion Binding /// Dna Binding	Nucleus
217234_s_at	VIL2	Villin 2 (Ezrin)	Cytoskeletal Anchoring /// Regulation Of Cell Shape	Structural Molecule Activity /// Cytoskeletal Protein Binding /// Protein Binding /// Binding	Cytoplasm /// Cytoskeleton /// Microvillus /// Membrane /// Actin Filament /// Cortical Cytoskeleton
1562955_at	WDFY1	Wd Repeat And Fyve Domain Containing 1	---	Phosphatidylinositol Binding /// Zinc Ion Binding /// Metal Ion Binding /// Zinc Ion Binding	Nucleus /// Early Endosome /// Cytosol
208743_s_at	YWHAB	Tyrosine 3-Monooxygenase/Tryptophan 5-Monooxygenase Activation Protein, Beta Polypeptide	---	Monooxygenase Activity /// Protein Domain Specific Binding /// Protein Binding /// Protein Binding	---
217741_s_at	ZA20D2	Zinc Finger, A20 Domain Containing 2	---	Dna Binding /// Zinc Ion Binding /// Metal Ion Binding	---
222357_at	ZBTB20	Zinc Finger And Btb Domain Containing 20	Transcription /// Regulation Of Transcription, Dna- Dependent	Dna Binding /// Protein Binding /// Zinc Ion Binding /// Metal Ion Binding	Nucleus
219062_s_at	ZCCHC2	Zinc Finger, Cchc Domain Containing 2	---	Nucleic Acid Binding /// Metal Ion Binding /// Zinc Ion Binding	---

A number of genes associated with viral response, cellular defense, and immune response genes were identified. A representative list of genes in the signature set is given in Table 3.

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Table 3: Representative genes in the signature set of chronic HCV infection:

<i>Probe Set ID</i>	<i>Gene Symbol</i>	<i>Gene Title</i>	<i>GO Biological Process</i>
201642_at	IFNGR2	Interferon Gamma Receptor 2	Response to virus
202086_at	MX1	Myxovirus (Influenza Virus) Resistance 1	Response to virus
202430_s_at	PLSCR1	Phospholipid Scramblase 1	Response to virus
203882_at	ISGF3G	Interferon-Stimulated Transcription Factor 3, Gamma 48Kda	Response to virus
204994_at	MX2	Myxovirus (Influenza Virus) Resistance 2	Response to virus
208436_s_at	IRF7	Interferon Regulatory Factor 7	Viral induction of host immune response, Response to virus
1553530_a_at	ITGB1	Integrin, Beta 1 (Fibronectin Receptor, Beta Polypeptide, Antigen Cd29 Includes Mdf2, Msk12)	Cellular defense response
<i>Probe Set ID</i>	<i>Gene Symbol</i>	<i>Gene Title</i>	<i>GO Biological Process</i>
1553530_a_at	ITGB1	Integrin, Beta 1 (Fibronectin Receptor, Beta Polypeptide, Antigen Cd29 Includes Mdf2, Msk12)	Cellular defense response
1555832_s_at	KLF6	Kruppel-Like Factor 6	B cell differentiation, regulation of transcription, DNA-dependent
200959_at	FUS	Fusion (Involved In T(12;16) In Malignant Liposarcoma)	Immune response
201762_s_at	PSME2	Proteasome (Prosome, Macropain) Activator Subunit 2 (Pa28 Beta)	Immune response
201786_s_at	ADAR	Adenosine Deaminase, Rna-Specific	Antimicrobial humoral response (sensu Vertebrata)
202086_at	MX1	Myxovirus (Influenza Virus) Resistance 1, Interferon-Inducible Protein P78 (Mouse) /// Myxovirus (Influenza Virus) Resistance 1, Interferon-Inducible Protein P78 (Mouse)	Immune response, response to virus

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GO= Gene Ontology

Example 5: VX-950 Normalizes the Signature Set Over the 14-Day**Treatment Period**

There was an observable trend in the gene expression levels normalizing towards healthy subject levels on dosing with VX-950. Delta expression levels were calculated as the mean ratio of interferon (IFN)-sensitive gene (ISG) expression levels for each patient (day 14 vs. day 0) shown on a $\log_{10}$ scale. Delta viral load was calculated as the ratio of viral load for each patient (day 0 vs. day 14) shown on a $\log_{10}$ scale. The correlation with healthy subject levels was determined for healthy subjects after 5 days of dosing with VX-950, and for HCV infected patients at pre-dosing, and after 7, 14, and 28 days of dosing with VX-950. The results are shown in FIG. 2.

Example 6: HCV Infection Enriches for Genes of Host Anti-Viral Gene**Categories**

In HCV infected subjects, the gene expression analysis revealed a significant over-representation of gene ontology (GO) categories related to host response to viral infection (Table 4). Also observed was a significant enrichment for known interferon-sensitive genes (ISG) ($p < 10^{-6}$) (where the p-value represents the probability that the enrichment of the genes in that functional category is random.)

Table 4: Signature set enriched for host anti-viral GO categories:

<i>Gene Ontology category</i>	<i>p-value</i>	<i># Genes altered</i>	<i># Genes on genechip</i>
<i>Immune response</i>	3.4×10^{-7}	30	566
<i>Response to biotic stimulus</i>	4.1×10^{-8}	36	705
<i>Response to stimulus</i>	7.7×10^{-8}	50	1230
<i>Defense response</i>	7.5×10^{-7}	31	620
<i>Response to pest, pathogen or parasite</i>	1.3×10^{-4}	19	378
<i>Response to stress</i>	1.0×10^{-5}	31	701
<i>Response to virus</i>	4.5×10^{-4}	6	51

Other genes in the signature set mapped to host immune response functions and other key biological functions related to a host of anti-viral defense mechanisms. For example, the genes mapped to functions related to organismal physiological processes; immune response; defense response; response to biotic stimulus; response to external stimulus; response to stimulus; response to external biotic stimulus; response to stress; response to pest, pathogen, or parasite; response to virus.

Example 7: Pre-Dose Expression Levels of IFN-Sensitive Genes Correlates with a Reduction in Plasma HCV RNA Levels

Table 5 shows the ratios of IFN-sensitive gene (ISG) expression levels between the enhanced responders and non-enhanced responders (the ratio is the level of expression of the enhanced responders over the levels of expression of the non-enhanced responders) prior to dosing with VX-950. The pre-dose expression levels of these genes correlates with plasma HCV RNA reduction.

Table 5: Ratios of ISG levels Between Enhanced Responders and Others

<i>Affymetrix Probeset ID</i>	<i>Gene Title</i>	<i>Gene Symbol</i>	<i>GO Biological Process Description</i>	<i>Ratio</i>
203153_at	Interferon-Induced Protein With Tetratricopeptide Repeats 1	IFIT1	Immune Response	8.57
204439_at	Interferon-Induced Protein 44-Like	IFI44L	---	4.17
213797_at	Radical S-Adenosyl Methionine Domain Containing 2	RSAD2	---	4.11
226757_at	Interferon-Induced Protein With Tetratricopeptide Repeats 2	IFIT2	Immune Response	3.48
204747_at	Interferon-Induced Protein With Tetratricopeptide Repeats 3	IFIT3	Immune Response	2.91
206332_s_at	Interferon, Gamma-Inducible Protein 16	IFI16	Immune Response, DNA-dependent Regulation Of Transcription	2.79
208966_x_at	Interferon, Gamma-Inducible Protein 16	IFI16	Immune Response, DNA-dependent Regulation Of Transcription	2.75
214453_s_at	Interferon-Induced Protein 44	IFI44	Immune Response	2.73
217502_at	Interferon-Induced Protein With Tetratricopeptide Repeats 2	IFIT2	Immune Response	2.73
203595_s_at	Interferon-Induced Protein With Tetratricopeptide Repeats 5	IFIT5	Immune Response	2.68
229450_at	Interferon-Induced Protein With Tetratricopeptide Repeats 3	IFIT3	Immune Response	2.46
208965_s_at	Interferon, Gamma-Inducible Protein 16	IFI16	Immune Response, DNA-dependent Regulation Of Transcription	2.45
203596_s_at	Interferon-Induced Protein With Tetratricopeptide Repeats 5	IFIT5	Immune Response	1.69
202446_s_at	Phospholipid Scramblase 1	PLSCR1	Response To Virus, Phospholipid Scrambling	1.42
202086_at	Myxovirus (Influenza Virus) Resistance 1	MX1	Immune Response, Signal Transduction	1.39
202411_at	Interferon, Alpha-Inducible Protein 27	IFI27	Immune Response	1.16
209417_s_at	Interferon-Induced Protein 35	IFI35	Immune Response	1.11
201601_x_at	Interferon Induced Transmembrane Protein 1 (9-27)	IFITM1	Immune Response, Negative Regulation Of Cell Proliferation	1.01
212203_x_at	Interferon Induced Transmembrane Protein 3 (1-8U)	IFITM3	Immune Response	1.01
201422_at	Interferon, Gamma-Inducible Protein 30	IFI30	Immune Response	0.93
214022_s_at	Interferon Induced Transmembrane Protein 1 (9-27)	IFITM1	Immune Response, Negative Regulation Of Cell Proliferation	0.93
201315_x_at	Interferon Induced Transmembrane Protein 2 (1-8D)	IFITM2	Immune Response	0.82

Example 8: Sustained Levels of Interferon-Sensitive Genes Correlate with a Reduction in Plasma HCV RNA Levels

The expression levels of selected interferon-sensitive genes (ISGs) were examined pre-dosing and at day 14 after dosing with VX-950 in HCV-infected enhanced responders and non-enhanced responders. The mean ratios of ISG expression levels (day 14 (d14) vs. pre-dose (d0)) are shown in FIG. 3A. There was a statistically significant difference in the sustained expression levels of the ISG between the two groups, wherein the enhanced responders had sustained levels of ISG expression. Genes that were outliers within each group are listed. Thus, in as little as 14 days, a comparison of baseline to day14 expression levels of ISGs can potentially predict VX-950 dosing outcomes.

FIG. 3B shows the change in expression levels and change in HCV viral load by day 14 as compared to day 0 in five enhanced responders (left-most bars) and 16 non-enhanced responders. The five enhanced responders, who had undetectable HCV RNA at day 14, had sustained levels of the IFN-sensitive genes (ISGs), as indicated by the minimal change in their expression levels.

FIG. 3C shows quantitative real-time PCR confirmation of the Affymetrix genechip results. Gene expression modulation of specific ISGs for each of the groups in 3B are shown (top left panel shows the results for the enhanced responders while the top right and bottom panels show the results for the non-enhanced responders). The overall trend confirms the genechip profiling data. There are also individual gene-level expression differences (e.g., GIP2, PLSCR) between the enhanced and non-enhanced responders.

From these results, it appears that sustained levels of interferon-induced genes in peripheral blood during VX-950 dosing were associated with best antiviral response.

Example 9: Signature sets of Specific HCV Subgroups

The signature set shown in Table 2 was obtained from a population of chronically infected HCV subjects without *a priori bias* using a unsupervised clustering method. A signature set for a selected group can be prepared based on the teachings provided herein. For example, a signature set can be generated for certain subgroups of HCV-infected subjects, for example: males, females, HCV genotype 1, 2, or 3, particular age groups,

ances, subjects that have responded well or poorly to previous treatments, subjects who have previously undergone a particular treatment, subjects who have not yet undergone treatment for HCV infection, subjects who have been diagnosed as being co-infected with another virus (e.g., hepatitis B and/or HIV), etc.

5 The information obtained from such analyses can be utilized as described herein.

A number of embodiments of the invention have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the invention. Accordingly, other embodiments are within the scope
10 of the following claims.

WHAT IS CLAIMED IS:

1. A method of evaluating a subject, the method comprising:
providing an evaluation of the expression of the genes in a signature set of genes
5 in the subject, wherein the signature set has the following properties:
it includes a plurality of genes each of which is differentially expressed as
between virally infected individuals and non-infected individuals,
it contains a sufficient number of differentially expressed genes such that
differential expression of each of the genes in the signature set in a subject is predictive
10 of infection with no more than about 15% false positives; and
providing a comparison of the expression of each of the genes in the set from the
subject with a reference value, thereby evaluating the subject.

2. The method of claim 1, wherein the comparison comprises comparing
15 expression in the subject with a non-infected reference and wherein differential
expression of each of the genes in the signature set of genes indicates a first state, and
differential expression of less than all of the genes in the signature set indicates a second
state.

20 3. The method of claim 2, wherein the first state comprises infection or a first
likelihood of infection.

4. The method of claim 2, wherein the second state comprises non-infection or a
second likelihood of infection.

25 5. The method of claim 1, wherein the reference is a value of expression from
one or more uninfected subjects.

6. The method of claim 1, wherein the comparison comprises comparing the
30 expression in the subject with an infected reference and wherein non-differential

expression of each of the genes in the signature set of genes indicates a first state, and non-differential expression of less than all of the genes in the signature set indicates a second state.

5 7. The method of claim 6, wherein the first state comprises infection or a first likelihood of infection.

 8. The method of claim 6, wherein the second state comprises non-infection or a second likelihood of infection.

10

 9. The method of claim 6, wherein the reference is a value of expression from one or more virally infected subjects.

 10. The method of claim 1, wherein peripheral blood from the subject is
15 evaluated.

 11. The method of claim 1, wherein the evaluating occurs prior to administering an inhibitor of a viral protease to the subject.

20 12. The method of claim 11, wherein the inhibitor is VX-950, SCH-503034, or BILN-261 (ciluprevir).

 13. The method of claim 1, wherein the evaluating occurs during the course of administering or after administering an inhibitor of a viral protease to the subject.

25

 14. The method of claim 13, wherein the inhibitor is VX-950, SCH-503034, or BILN-261 (ciluprevir).

 15. The method of claim 1, wherein the method comprises determining a post
30 administration level of gene expression, determined for an interferon sensitive gene (ISG) in the subject to provide a post administration determined value; and

comparing the post administration determined value with a reference value,
thereby evaluating the subject.

16. The method of claim 15, wherein the reference value comprises the level of
5 expression of the ISG prior to administration of the antiviral treatment.

17. The method of claim 1, wherein the signature set of genes comprises a
plurality of genes associated with hepatitis C virus (HCV) infection.

10 18. The method of claim 1, wherein the signature set of genes comprises at least
about 10% of the genes listed in Table 2.

19. The method of claim 1, wherein the signature set of genes comprises a gene
from one or more of the following categories: organismal physiological processes;
15 immune response; defense response; response to biotic stimulus; response to stimulus;
response to stress; response to pest, pathogen, or parasite; or response to virus.

20. The method of claim 1, wherein the signature set of genes comprises one or
more interferon-sensitive genes (ISG).

20

21. The method of claim 20, wherein the ISG is selected from the group
consisting of: IFIT1, RSAD2, IFIT2, IFI16, IFI44, IFIT2, IFIT5, PLSCR1, IFIT3, IFI35,
IFITM1, IFITM3, IFI30, IFITM1, IFITM2, GIP2, OAS3, IFIT3, MX1, IFIL44L, IFI27,
IFIT2A, PRSAD, or IFITA.

25

22. The method of claim 20, wherein the signature set of genes comprises at least
1 of: GIP2, OAS3, IFIT3, MX1, IFIL44L, PLSCR1, IFI27, IFIT2A, PRSAD, or IFITA.

23. A method of evaluating the efficacy of a treatment of HCV infection in a
30 subject, the method comprising:
administering the treatment;

performing the evaluation of claim 1,
thereby evaluating the efficacy of the treatment.

24. A method of evaluating the efficacy of a drug for use in treatment of HCV
infection in a subject, the method comprising:

providing a determination of a first level of gene expression associated with HCV
infection in the subject at a first time point;

providing a determination of a second level of gene expression in the subject at a
second time point; and

providing a comparison of the first and second levels of gene expression, wherein
sustained levels of gene expression between the first and second time points is indicative
of drug efficacy.

25. The method of claim 24, wherein the comparison of the first and second
levels of gene expression comprises comparing the levels of one or more interferon-
sensitive genes (ISG).

26. The method of claim 25, wherein the ISG is selected from the group
consisting of: IFIT1, RSAD2, IFIT2, IFI16, IFI44, IFIT2, IFIT5, PLSCR1, IFIT3, IFI35,
IFITM1, IFITM3, IFI30, IFITM1, IFITM2, GIP2, OAS3, IFIT3, MX1, IFIL44L, IFI27,
IFIT2A, PRSAD, or IFITA.

27. The method of claim 25, wherein first and second levels of at least 1 of:
GIP2, OAS3, IFIT3, MX1, IFIL44L, PLSCR1, IFI27, IFIT2A, PRSAD, or IFITA are
compared.

28. A method of evaluating the efficacy of a drug for use in treatment of HCV
infection in a subject, the method comprising:

providing a determination of a first level of gene expression associated with HCV
infection in the subject at a first time point;

providing a determination of a second level of gene expression in the subject at a second time point; and

providing a comparison of the first and second levels of gene expression to a control level of gene expression, wherein a smaller difference between the second level
5 and the control level as compared to the difference between the first level and the control level is indicative of drug efficacy.

29. The method of claim 28, wherein the gene expression associated with HCV infection is determined for a plurality of the genes listed in Table 2.

10

30. The method of claim 29, wherein the plurality comprises at least about 10% of the genes listed in Table 2.