

WHAT IS CLAIMED IS:

- 1                   1.       A method for assessing a biochemical response to a glucocorticoid  
2    receptor antagonist (GRA) in a human subject, the method comprising:  
3                   a) measuring a first amount, or activity of 51 kDa FK506 binding protein  
4    (FKBP5 protein) or a first expression level of a gene encoding FKBP5 protein in a first  
5    sample from the subject, wherein:  
6                   i) the first sample comprises primary cells; and  
7                   ii) the first sample is obtained before the GRA is administered to the  
8    subject;  
9                   b) measuring a second amount or activity of FKBP5 protein or a second  
10   expression level of a gene encoding FKBP5 protein in a second sample from the subject,  
11   wherein:  
12                  i) the second sample comprises primary cells; and  
13                  ii) the second sample is obtained after the GRA is administered to the  
14   subject; and  
15                  d) comparing the first and second amounts, activities, or expression levels,  
16   wherein a reduction in the amount or activity of FKBP5 protein or a reduction in the  
17   expression level of the gene encoding FKBP5 protein in the second sample indicates the  
18   biochemical response to the GRA.
- 1                   2.       The method of claim 1, wherein the first sample is obtained prior to  
2    administering multiple doses of GRA to the subject, and the second sample is obtained after  
3    administering the multiple doses of GRA to the subject.
- 1                   3.       The method of claim 1, wherein the measuring of a) and/or b)  
2    comprises quantitating an amount of mRNA encoding FKBP5 protein in the sample.
- 1                   4.       The method of claim 1, wherein the measuring of a) and/or b)  
2    comprises quantitating the amount of FKBP5 protein in the sample.
- 1                   5.       The method of claim 1, wherein the measuring comprises quantitating  
2    the amount of FKBP5 protein activity in the sample.

1                   6.     The method of claim 5, wherein the quantitating the amount of FKBP5  
2     protein activity in the sample comprises measuring FKBP5 protein peptidyl-prolyl-cis-trans  
3     isomerase activity in the sample.

1                   7.     The method of claim 5, wherein the quantitating the amount of FKBP5  
2     protein activity in the sample comprises measuring the amount of FKBP5 protein bound to  
3     glucocorticoid receptor (GR) in the sample.

1                   8.     The method of claim 1, wherein the GRA administered to the subject  
2     comprises mifepristone.

1                   9.     The method of claim 1, wherein the GRA administered to the subject is  
2     not mifepristone.

1                   10.    The method of claim 9, wherein the GRA administered to the subject  
2     comprises a heteroaryl-ketone GRA.

1                   11.    The method of claim 1, wherein the first or second samples comprise  
2     whole blood, or a fraction thereof.

1                   12.    The method of claim 1, wherein the first or second samples comprise  
2     nasal epithelial scraping samples.

1                   13.    The method of claim 1, wherein the patient is in need of administration  
2     of the glucocorticoid receptor antagonist (GRA).

1                   14.    The method of claim 13, wherein the patient has elevated levels of  
2     cortisol.

1                   15.    The method of claim 1, wherein the patient has cancer and the first and  
2     second samples comprise tumor cells.

1                   16.    The method of claim 1, wherein the first and second samples comprise  
2     whole blood, or a fraction thereof.

1                   17.    The method of claim 1, wherein the method comprises administering  
2     an increased amount of GRA to the subject in the absence of a detected reduction in the

3 amount or activity of FKBP5 protein or a detected reduction in the expression level of the  
4 gene encoding FKBP5 protein in the second sample.

1 18. A method for diagnosing Cushing's syndrome in a human subject, the  
2 method comprising:

3 a) measuring an amount, or activity of 51 kDa FK506 binding protein (FKBP5  
4 protein) or an expression level of a gene encoding FKBP5 protein in a sample obtained from  
5 the subject, wherein the sample comprises primary cells; and

6 b) identifying the subject as likely to be suffering from Cushing's syndrome  
7 when the amount, activity or expression level is high relative to a control.

1 19. The method of claim 18, wherein the measuring comprises quantitating  
2 an amount of mRNA encoding FKBP5 protein in the primary cells of the sample.

1 20. The method of claim 18, wherein the measuring comprises quantitating  
2 the amount of FKBP5 protein in the primary cells of the sample.

1 21. The method of claim 18, wherein the measuring comprises quantitating  
2 the FKBP5 protein activity in the primary cells of the sample.

1 22. The method of claim 21, wherein the quantitating the FKBP5 protein  
2 activity in the primary cells of the sample comprises quantitating FKBP5 protein peptidyl-  
3 prolyl-cis-trans isomerase activity in the primary cells of the sample.

1 23. The method of claim 21, wherein the quantitating the FKBP5 protein  
2 activity in the primary cells of the sample comprises quantitating the amount of FKBP5  
3 protein bound to GR in the primary cells of the sample.

1 24. The method of claim 18, wherein the sample obtained from the subject  
2 comprises whole blood, or a fraction thereof.

1 25. The method of claim 18, wherein the subject has undergone  
2 transsphenoidal surgery before the sample is obtained from the subject.

1 26. The method of claim 18, wherein the method comprises administering  
2 a treatment for Cushing's syndrome when the amount or activity of FKBP5 protein or the  
3 expression level of the gene encoding FKBP5 protein is high relative to a control.

- 1                   27.     The method of claim 26, wherein the administering the treatment for  
2     Cushing's syndrome comprises administering to the subject a glucocorticoid receptor  
3     antagonist (GRA).
- 1                   28.     A method for assessing a biochemical response in a human subject to  
2     administering to the subject a medical or surgical therapy for treatment of hypercortisolemia,  
3     the method comprising:  
4                   a) measuring a first amount, or activity of 51 kDa FK506 binding protein  
5     (FKBP5 protein) or a first expression level of a gene encoding FKBP5 protein in a first  
6     sample from the subject, wherein:  
7                   i) the first sample comprises primary cells; and  
8                   ii) the first sample is obtained before administering the medical or  
9     surgical therapy for treatment of hypercortisolemia to the subject;  
10                  b) measuring a second amount or activity of FKBP5 protein or a second  
11     expression level of a gene encoding FKBP5 protein in a second sample from the subject,  
12     wherein:  
13                  i) the second sample comprises primary cells; and  
14                  ii) the second sample is obtained after the medical or surgical therapy  
15     for treatment of hypercortisolemia is administered to the subject; and  
16                  d) comparing the first and second amounts, activities, or expression levels,  
17                  wherein a reduction in the amount or activity of FKBP5 protein or a reduction  
18     in the expression level of the gene encoding FKBP5 protein in the second sample indicates  
19     the biochemical response to the medical or surgical therapy for treatment of  
20     hypercortisolemia.
- 1                   29.     The method of claim 28, wherein the medical or surgical therapy for  
2     treatment of hypercortisolemia is selected from the group consisting of: inhibition of  
3     steroidogenesis, administration of an ACTH modulator, GRA administration, transsphenoidal  
4     surgery, repeat transsphenoidal surgery, unilateral adrenalectomy, bilateral adrenalectomy,  
5     radiotherapy, resection of a non-pituitary ACTH-secreting tumor, treatment with a peptide  
6     receptor radionuclide therapy, and combinations thereof.

1                   30.     The method of claim 29, wherein the inhibition of steroidogenesis  
2     comprises administration of ketoconazole, levoketoconazole, metyrapone, LCI699, mitotane,  
3     aminoglutethimide, etomidate, or a combination thereof.

1                   31.     The method of claim 29, wherein the administration of an ACTH  
2     modulator comprises administration of a dopamine agonist, somatostatin, a somatostatin  
3     analog, retinoic acid, R-roscovitine, or a combination thereof.

1                   32.     The method of claim 31, wherein the dopamine agonist is selected  
2     from the group consisting of bromocriptine and cabergoline.

1                   33.     The method of claim 28, wherein the method comprises administering  
2     an additional medical or surgical therapy for treatment of hypercortisolemia in an absence of  
3     a detected reduction in the amount or activity of FKBP5 protein or reduction in the  
4     expression level of the gene encoding FKBP5 protein in the second sample.

1