STAMP, a novel modulator of steroid receptor-mediated gene induction and gene repression

Description of Technology:

A novel factor, SRC-1 and TIF-2 Associated Modulatory Protein (STAMP), has been found to modulate steroid hormone-responsive gene expression. STAMP lowers the concentration of steroid needed to induce (or repress) target genes and thereby offers a novel approach for reducing the severity of unwanted side effects. It thus increases the number of situations in which steroid hormone therapies can be employed. Use of STAMP polypeptides also modulates the dose-response curve for a steroid.

Steroid hormones such as androgens, glucocorticoids, progestins and mineralocorticoids are used to treat many diseases. They act to regulate many physiological responses by binding to steroid receptors. However, because steroid receptors are expressed in many tissues, therapeutic efforts to modify the effects of steroid hormones on a specific tissue or on a specific receptor of the steroid receptor family often cause undesirable effects in other tissues or on other receptors. One potential approach to reduce the side effects is to lower the concentration of steroid used while maintaining the level of steroid-mediated response. This effect has been shown to occur on administration of STAMP. STAMP also increases the residual agonist activity of antiglucocorticoids and antiprogestins and thus provides a new approach to modifying the properties of selective receptor modulators in antihormone therapies.

Applications:

- Diseases requiring chronic steroid treatment such as rheumatoid arthritis, psoriatic arthritis, asthma, inflammatory and auto-immune diseases
- Diseases characterized by excess or deficiency of glucocorticoids such as obesity, diabetes, hypertension, Cushing's Syndrome, Parkinson's Disease, Addison's Disease
- Diseases in which glucocorticoid-responsive gene expression is deranged, such as carbohydrate, protein or lipid metabolism
- Diseases where mineralocorticoid-regulated genes are involved
- Cancers responsive to androgens such as prostate cancer
- Where shifting the dose-response curve would reduce the amount of steroid hormone required and decrease the side-effects of steroid hormone and antihormone therapies
- Therapeutic applications related to male or female hormone replacement, symptoms related to menopause, birth control, menstrual cycle/amenorrhea, fertility or endometriosis

Advantages:

- STAMP reduces the severity of unwanted side effects of steroid hormone therapies
- STAMP modulates the gene induction properties of androgen and progesterone receptors
- STAMP modulates both the gene induction and repression properties of glucocorticoid receptors
- STAMP increases the agonist character of antiglucocorticoids and antiprogestins
- STAMP is predicted to modify mineralocorticoid-regulated gene expression
- STAMP is inactive toward estrogen receptors α and β, thyroid receptor β, PPARγ, retinoid receptor α and RXR α
- STAMP siRNAs may be useful as therapeutics
- STAMP polypeptides may be useful as therapeutics

Market:

The protein STAMP offers a novel approach for reducing the severity of unwanted side effects of steroid hormone therapies. Therefore, STAMP may be helpful in the treatment of diseases requiring chronic steroid treatments, those characterized by excess or deficiency of glucocorticoid response, therapies related to male or female hormone replacement or cancers responsive to androgens. Similarly, STAMP can reduce the generalized repression of steroid hormone action that is usually encountered in endocrine therapies with antisteroids. Companies interested in the reformulation of existing therapeutics to take advantage of the potential of STAMP to shift the dose-response curve or modify the potency of their existing compounds as well as those interested in development of new drugs would be interested in this technology.

Development Status:

- STAMP, a protein that is a novel nuclear receptor cofactor, has been identified and shown to modify the magnitude of, and position of the dose-response curve for steroid receptor-mediated gene expression (both induction and repression) and the amount of agonist activity of selective receptor modulators (SRM), or antisteroids with residual agonist activity
- STAMP siRNAs have been shown to change the total amount of gene expression, and the position of the dose-response curve of endogenous glucocorticoid receptor induced genes
- A fragment of STAMP retains most of its modulatory activity
- Ongoing studies are defining the domains of STAMP and its associated factors that are required to mediate STAMP actions
- Two STAMP antibodies have been prepared
- Mouse ES cells containing a conditional knockout of the STAMP gene have been prepared in preparation for making STAMP knockout mice

Further Research & Development Required:

- Further *in vivo* studies of the role of STAMP in glucocorticoid receptor-mediated repression
- Further study of the activity of STAMP with endogenous target genes of glucocorticoid, progesterone, and androgen receptor-mediated responses
- Investigation of the mechanism of action of STAMP
- Studies on the regulation of STAMP levels and activities in intact cells and organisms
- Development of STAMP knockout mouse

Inventors:

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Publications:

He Y, Simons SS Jr Mol Cell Biol. 27, 1467-1485 [2007]. *STAMP: A Novel Predicted Factor Assisting TIF2 Actions in Glucocorticoid Receptor –mediated Induction and Repression [pubmed reference]*

Patent Status:

DHHS Reference No E-056-2004, PCT Application Serial Number PCT/US2005/006393

Licensing Status:

Available for exclusive or non-exclusive licensing

Licensing Contact:

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Collaborative Research Opportunity:

The National Institute of Diabetes and Digestive Diseases, Laboratory of Molecular and Cellular Biology is seeking parties interested in collaborative research to further evaluate the role of STAMP in glucocorticoid receptor-mediated repression, to investigate the mechanism of action of the protein, and to conduct further studies on the regulation of STAMP levels and activities in intact cells and model organisms. Please contact Dr. Stoney Simons at steroids@helix.nih.gov or Rochelle S. Blaustein at Rochelle.Blaustein@nih.gov for more information.

Research Focus and Selected Publications for Principal Investigator

S. Stoney Simons Jr., Ph.D Chief, Steroid Hormones Section

The major focus of Dr. Simon's laboratory is the investigation of the initial events of steroid hormone action. These events include the equilibrium interactions of cofactors with agonist- and antagonist-bound receptors and the modulation of receptor-mediated gene transcription properties by novel pathways and cofactors.

1. Simons SS Jr How much is enough? Modulation of dose-response curve for steroid receptor-regulated gene expression by changing concentrations of transcription factor. *Current Topics in Medicinal Chemistry* (6) 271-285, 2006. [Full Text/Abstract]

2. Kim Y Sun Y Chow C Pommier YG Simons SS Jr Effects of acetylation, polymerase phosphorylation, and DNA unwinding in glucocorticoid receptor transactivation. *J Steroid Biochem Molec Biol* (100) 3-17, 2006. [Full Text/Abstract]

3. Wang D, Simons SS Jr Corepressor Binding to Progesterone and Glucocorticoid Receptors Involves the AF-1 Domain and is Inhibited by Molybdate. *Mol Endocrinol*, 2005. [Full Text/Abstract]

4. Cho S, Kagan BL, Blackford JA Jr Szapary D, Simons SS Jr Glucocorticoid receptor ligand binding domain is sufficient for the modulation of glucocorticoid induction properties by homologous receptors, coactivator transcription intermediary factor 2, and Ubc9. *Mol Endocrinol* (19): 290-311, 2005. [Full Text/Abstract]

5. Cho S, Blackford JA Jr, Simons SS Jr Role of activation function domain-1, DNA binding, and coactivator GRIP1 in the expression of partial agonist activity of glucocorticoid receptor-antagonist complexes. *Biochemistry* (44): 3547-61, 2005. [Full Text/Abstract]

6. Wang Q Blackford JA Jr Song LN Huang Y Cho S Simons SS Jr Equilibrium interactions of corepressors and coactivators with agonist and antagonist complexes of glucocorticoid receptors. *Mol Endocrinol* (18): 1376-95, 2004. [Full Text/Abstract]

7. Wang Q Anzick S Richter WF Meltzer P Simons SS Jr Modulation of transcriptional sensitivity of mineralocorticoid and estrogen receptors. *J Steroid Biochem Mol Biol* (91): 197-210, 2004. [Full Text/Abstract]

8. Chen J Blackford JA Jr Simons SS Jr PCR expression mutagenesis: a high-throughput mutation assay applied to the glucocorticoid receptor ligand-binding domain. *Biochem Biophys Res Commun* (321): 893-9, 2004. [Full Text/Abstract]

9. Chen J He Y Simons SS Jr Structure/activity relationships for GMEB-2: the second member of the glucocorticoid modulatory element-binding complex. *Biochemistry* (43): 245-55, 2004. [Full Text/Abstract]