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(54) Titre : PROTEINES KINASES HUMAINES hYAK3
(54) Title: HUMAN PROTEIN KINASES hYAK3

Nucleotide and Amino Acid sequence from a hYAK3α (SEQ ID NOS: 1 and 2, respectively.)

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1  GGAGCGAAATGCGCTGAGCTGCAGTGTCTGCTGAGAGTACCCCTGGGAGCCCTCCGCGG  60
61  CGGAGGCGAGCCCTCCGCGCTAGGTGGCGTGGCGGACCCCTAAGCTGGCGACCTCTC  120
121  CCGCGCGCGGGCTCCGAGCTAGGAGATGGGAGGACAGCTCCTGGGCTGGGCGGAAGGA  180
      M G G T A R G P G R K D
181  TCCGCGCGCGCCCTGGGCGCGGGCTCCGCGCCCGGAGCGAGGCTTGGGGATGGTGTCTA  240
      A G P P G A G L P P Q Q R R L G D G V
241  TGACACCTTCATGATGATAGATGAACCAAAATGTCGCCCTCTTCAAAATGATCTGTGCAA  300
      D T F M M I D E T K C P P C S N V L C H
301  TCCTTCTGAACCACTCCGCGGAGAGACTAAATATGACCACTGAGCGATTTACAGGAGA  360
      P S E P P P P R R L N M T T E Q P T G D
361  TCATACTCAGCAGCTTTTGGATGGAGGTGAGATGAAGTAGAAGACAGCTGTTTCAAGAATT  420
      H T Q H F L D G G E M K V E Q L F Q E F
421  TGGCAACAGAAATCCAACTACTATTCAGTCAGATGGCATCACTGACTCTGAAATATGCTC  480
      G N R K S N T I Q S D G I S D S E X C S
481  TCCTACTGTTCTCAGGTAAGAGTTCAGATTTGCTTGAATACAGTAARATCCAAAGTTTC  540
      P T V S Q G K S S D C L N T V K S N S S
541  ATCCAAAGGACCCCAAGTGGTCCCTCTGACTCCAGAACAGCCCTGAGGCAATATAACA  600
      S K A P K V V P L T P E Q A L K Q Y X H
601  CCACCTCACTGCTATGAGAACTGGAAATTAATTAATATCCAGAAATTTACTTTGTAGG  660
      H L T A Y E K L E I I N Y P E I Y F V G
661  TCCAAATGCCAAGAAAGACATGGAGTTATTTGGTGGTCCCAATATAGAGGTATGATGA  720
      P N A K K R H G V I G G P N N G G Y D D
721  TGCAGATGGGGCTATATTCTATCTGCTCAGAGCATCTAGCTTATCATATGAGGTGCT  780
      A D Q A Y I H V P R D H L A Y R Y E V L
781  GAAATATTGGCAAGGGAGTTTGGGAGGTGGCCAGGCTCTATGATCAGAACTTCG  840
      K I I G K G S F G Q V A R V Y D H K L R
841  ACAGTACCTGGGCTAAAGTGGTGGCAATGAGAGCGCTTCTATCTCAAGCACTGA  900
      Q Y V A L K M V R N E K R F H R Q A A E
901  CGAGATCCGGAATTTGGAGCATCTTAAGAAGACAGATTAAGCTGGTAGTATGAACCTTAT  960
      E I R I L E H L K K Q D K T G S M N V I
961  CCACRTGCTGAAAGTTTCACATTCGGAAGCAGTGTTCGATGGGCTTTGAATTCGTGAG  1020
      H M L E S F T F R N H V C H A F E L L S
1021  CATAGAGCTTTATGAGCTGATTAAGAAATAAGTTTCAGGTTTATGAGCTTCAGTTGCT  1080
      I D L Y E L I K K N K F Q G P S V Q L V
1081  ACGCAAGTTTCCAGTCCATCTTCAATCTTGGATGCTCCGCAAGAAATAGATATAT  1140
      R K F A Q S I L Q S L D A L H K N K T I
1141  TCACTGCGATCTGAAGCAGAAACATTTCTCTGAACACACGCGGCGAGTTCAACCAA  1200
      H C D L K P R N I L L K H H G R S S T K
1201  GGTCAATTGACTTTGGGTCCAGCTGTTTCCAGTACCAAGAGCTCTACACATATATCCAGTC  1260
      V I D F G S S C F E Y Q K L Y T Y I Q S
1261  TCGGTTCTACAGAGCTCCAGAAATCATCTTAGGAAGCGGCTACAGCACCAATTGACAT  1320
      R F Y R A P E I I L G S R Y S T P I D I
1321  ATGGAGTTTGGCTGCATCTTGGCAGAACTTTTACAGGACAGCTCTCTTCCCTGGAGA  1380
      W S F G C I L A E L L T G Q P L F P G E
1381  GGATGAAGGAGACAGTTGGCTCCATGATGGAGCTTATAGGATGCCACCAAAACT  1440
      D E G D Q L A S M M E L L G M P P P K L
1441  TGTGAGCAATCAAACTGGCAAGTACTTTATTAATTCGAAGGACATACCCGCTACTG  1500
      L E Q S K R A K Y F I N S K G I P R Y C
1501  CTCCTGTGACTACCCAGGAGATGGGAGGGTTGTGCTTGTGGGGGTGCTCACTACCTAGGG  1560
      S V T T Q A D G R V V L V G G R S R R G
1561  TAAAGAGCGGGTCCCGAGGAGCAAGACTGGGGACAGCACTGAAGGGTGTGATGA  1620
      K K R G P P G S K D W G T A L K G C D D
1621  CTACTTGTATTAGAGTCTTGAAGGTGTCTTCACTGGGACCCCTCTGCCCGCTTGAC  1680
      Y L F I E F L K R C L H N D P S A R L T
1681  CCCAGCTCAGCATTAAGACACCTTTGGATTAGCAAGTCTTCTCCCGAGACCTCTCACAC  1740
      F A Q A L R H P W I S K S V F R P L T T
1741  CATAGACAGGTGTGAGGAAACGGGTAGTTAATCTGCAAGTGTCTTCCAGGGATTGGG  1800
      I D K V S G K R V V N P A S A F Q G L G
1801  TTCTAAGCTGCCCTCAGTGTGGATAGCCAAAGCTTAAGGCTAAGCTTAATGTCAGA  1860
      S K L P F V V G I A N K L K A N L M S E
1861  AACCAGTGTAGTATACCCGTATGCAGTGTATTGCCAAAACTGATTAGCTAGTGGACAGA  1920
      T N G S I P L C S V L P K L I S
1921  GATATGCCAGAGATGCATATGTGTATATTTATGATCTTACAAACCTGCAAAATGGAAA  1980
1981  AATGCAAGCCCATTTGGTGATTTTTTTGTAGAGTAGACCTTTTTTAAACAAGACAAA  2040
2041  CATTTTATATGATATAAAAA  2061
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(57) Abrégé/Abstract:

hYAK3 polypeptides and polynucleotides and methods for producing such polypeptides by recombinant techniques are disclosed. Also disclosed are methods for utilizing hYAK3 polypeptides and polynucleotides in the design of protocols for the treatment of bone loss including osteoporosis; inflammatory diseases such as Adult Respiratory Disease Syndrome (ARDS),



(57) Abrégé(suite)/Abstract(continued):

Rheumatoid arthritis, Osteoarthritis, Inflammatory Bowel Disease (IBD), psoriasis, dermatitis, asthma, allergies; infections such as bacterial, fungal, protozoan and viral infections, particularly infections caused by HIV-1 or HIV-2; HIV-associated cachexia and other immunodeficiency disorders; septic shock; pain; injury; cancers including testicular cancer; anorexia; bulimia; Parkinson's disease; cardiovascular disease including restenosis, atherosclerosis, acute heart failure, myocardial infarction; hypotension; hypertension; urinary retention; angina pectoris; ulcers; benign prostatic hypertrophy; and psychotic and neurological disorders, including anxiety, schizophrenia, manic depression, delirium, dementia, severe mental retardation and dyskinesias, such as Huntington's disease or Gilles de la Tourette's syndrome., among others, and diagnostic assays for such conditions.

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ABSTRACT OF THE DISCLOSURE

hYAK3 polypeptides and polynucleotides and methods for producing such polypeptides by recombinant techniques are disclosed. Also disclosed are methods for utilizing hYAK3

5 polypeptides and polynucleotides in the design of protocols for the treatment of bone loss including osteoporosis; inflammatory diseases such as Adult Respiratory Disease Syndrome (ARDS), Rheumatoid arthritis, Osteoarthritis, Inflammatory Bowel Disease (IBD), psoriasis, dermatitis, asthma, allergies; infections such as bacterial, fungal, protozoan and viral infections, particularly infections caused by HIV-1 or HIV-2; HIV-associated cachexia and other

10 immunodeficiency disorders; septic shock; pain; injury; cancers including testicular cancer; anorexia; bulimia; Parkinson's disease; cardiovascular disease including restenosis, atherosclerosis, acute heart failure, myocardial infarction; hypotension; hypertension; urinary retention; angina pectoris; ulcers; benign prostatic hypertrophy; and psychotic and neurological disorders, including anxiety, schizophrenia, manic depression, delirium, dementia, severe mental retardation and

15 dyskinesias, such as Huntington's disease or Gilles de la Tourette's syndrome., among others, and diagnostic assays for such conditions.

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Human Protein Kinases hYAK3

FIELD OF INVENTION

5 This invention relates to newly identified polynucleotides, polypeptides encoded by them and to the use of such polynucleotides and polypeptides, and to their production. More particularly, the polynucleotides and polypeptides of the present invention relate to a serine/threonine protein kinase, hereinafter referred to as hYAK3. The invention also relates to inhibiting or activating the action of such polynucleotides and polypeptides.

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BACKGROUND OF THE INVENTION

A number of polypeptide growth factors and hormones mediate their cellular effects through a signal transduction pathway. Transduction of signals from the cell surface receptors for these ligands to intracellular effectors frequently involves phosphorylation or dephosphorylation of specific protein substrates by regulatory protein serine/threonine kinases (PSTK) and phosphatases. Serine/threonine phosphorylation is a major mediator of signal transduction in multicellular organisms. Receptor-bound, membrane-bound and intracellular PSTKs regulate cell proliferation, cell differentiation and signalling processes in many cell types.

Aberrant protein serine/threonine kinase activity has been implicated or is suspected in a number of pathologies such as rheumatoid arthritis, psoriasis, septic shock, bone loss, many cancers and other proliferative diseases. Accordingly, serine/threonine kinases and the signal transduction pathways which they are part of are potential targets for drug design.

A subset of PSTKs are involved in regulation of cell cycling. These are the cyclin-dependent kinases or CDKs (Peter and Herskowitz, Cell 1994: 79, 181-184). CDKs are activated by binding to regulatory proteins called cyclins and control passage of the cell through specific cell cycle checkpoints. For example, CDK2 complexed with cyclin E allows cells to progress through the G1 to S phase transition. The complexes of CDKs and cyclins are subject to inhibition by low molecular weight proteins such as p16 (Serrano et al, Nature 1993: 366, 704), which binds to and inhibits CDK4. Deletions or mutations in p16 have been implicated in a variety of tumors (Kamb et al, Science 1994: 264, 436-440). Therefore, the proliferative state of cells and diseases associated with this state are dependent on the activity of CDKs and their associated regulatory molecules. In diseases such as cancer where inhibition of proliferation is desired, compounds that inhibit CDKs may be useful therapeutic agents. Conversely, activators of CDKs may be useful where enhancement of proliferation is needed, such as in the treatment of immunodeficiency.

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YAK1, a PSTK with sequence homology to CDKs, was originally identified in yeast as a mediator of cell cycle arrest caused by inactivation of the cAMP-dependent protein kinase PKA (Garrett et al, Mol Cell Biol. 1991: 11, 4045-4052). YAK1 kinase activity is low in cycling yeast but increases dramatically when the cells are arrested prior to the S-G2 transition. Increased expression
 5 of YAK1 causes growth arrest in yeast cells deficient in PKA. Therefore, YAK1 can act as a cell cycle suppressor in yeast.

Frequently, in disease such as osteoporosis and osteoarthritis, patients have established lesions of bone or cartilage, respectively. Treatment of such lesions requires an agent that will stimulate new bone or cartilage formation to replace that lost to the disease; therefore, there is a need
 10 for drugs that increase the number of osteoblasts or chondrocytes, the cells responsible for bone or cartilage formation, respectively. Similarly, replacement of heart or skeletal muscle depleted by diseases such as myocardial infarction or HIV-associated cachexia requires drugs that stimulate proliferation of cardiac myocytes or skeletal myoblasts. The present invention describes a novel human homolog of yeast YAK1 termed hYAK3, which is expressed predominantly in testis and
 15 skeletal muscle. The sequence of hYAK3 shares homology with predicted PSTK's from *C. elegans*, *S. pombe* and *S. cerevisiae* and has motifs associated with known protein kinases. Inhibitors of hYAK3 are expected to stimulate proliferation of cells in which it is expressed.

This indicates that these serine/threonine protein kinases have an established, proven history as therapeutic targets. Clearly there is a need for identification and characterization of further
 20 members of the serine/threonine protein kinase family which can play a role in preventing, ameliorating or correcting dysfunctions or diseases, including, but not limited to, bone loss including osteoporosis; inflammatory diseases such as Adult Respiratory Disease Syndrome (ARDS), Rheumatoid arthritis, Osteoarthritis, Inflammatory Bowel Disease (IBD), psoriasis, dermatitis, asthma, allergies; infections such as bacterial, fungal, protozoan and viral infections, particularly
 25 infections caused by HIV-1 or HIV-2; HIV-associated cachexia and other immunodeficiency disorders; septic shock; pain; injury; cancers including testicular cancer; anorexia; bulimia; Parkinson's disease; cardiovascular disease including restenosis, atherosclerosis, acute heart failure, myocardial infarction; hypotension; hypertension; urinary retention; angina pectoris; ulcers; benign prostatic hypertrophy; and psychotic and neurological disorders, including anxiety, schizophrenia,
 30 manic depression, delirium, dementia, severe mental retardation and dyskinesias, such as Huntington's disease or Gilles de la Tourette's syndrome..

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SUMMARY OF THE INVENTION

In one aspect, the invention relates to hYAK3 polypeptides and recombinant materials and methods for their production. Another aspect of the invention relates to methods for using such hYAK3 polypeptides and polynucleotides. Such uses include the treatment of bone loss including

5 osteoporosis; inflammatory diseases such as Adult Respiratory Disease Syndrome (ARDS), Rheumatoid arthritis, Osteoarthritis, Inflammatory Bowel Disease (IBD), psoriasis, dermatitis, asthma, allergies; infections such as bacterial, fungal, protozoan and viral infections, particularly infections caused by HIV-1 or HIV-2; HIV-associated cachexia and other immunodeficiency disorders; septic shock; pain; injury; cancers including testicular cancer; anorexia; bulimia;

10 Parkinson's disease; cardiovascular disease including restenosis, atherosclerosis, acute heart failure, myocardial infarction; hypotension; hypertension; urinary retention; angina pectoris; ulcers; benign prostatic hypertrophy; and psychotic and neurological disorders, including anxiety, schizophrenia, manic depression, delirium, dementia, severe mental retardation and dyskinesias, such as Huntington's disease or Gilles de la Tourette's syndrome., among others. In still another aspect, the

15 invention relates to methods to identify agonists and antagonists using the materials provided by the invention, and treating conditions associated with hYAK3 imbalance with the identified compounds. Yet another aspect of the invention relates to diagnostic assays for detecting diseases associated with inappropriate hYAK3 activity or levels.

20 BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the nucleotide and deduced amino acid sequence from human hYAK3 α .
SEQ ID NOS: 1 and 2.

Figure 2 shows the nucleotide and deduced amino acid sequence from human hYAK3 β .
SEQ ID NOS: 3 and 4.

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DESCRIPTION OF THE INVENTION

Definitions

The following definitions are provided to facilitate understanding of certain terms used frequently herein.

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"hYAK3" refers, among others, generally to a polypeptide having the amino acid sequence set forth in SEQ ID NO:2 or 4 or an allelic variant thereof.

"hYAK3 activity or hYAK3 polypeptide activity" or "biological activity of the hYAK3 or hYAK3 polypeptide" refers to the metabolic or physiologic function of said hYAK3 including

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similar activities or improved activities or these activities with decreased undesirable side-effects. Also included are antigenic and immunogenic activities of said hYAK3.

"hYAK3 gene" refers to a polynucleotide having the nucleotide sequence set forth in SEQ ID NO:1 or 3 or allelic variants thereof and/or their complements.

5 "Antibodies" as used herein includes polyclonal and monoclonal antibodies, chimeric, single chain, and humanized antibodies, as well as Fab fragments, including the products of an Fab or other immunoglobulin expression library.

"Isolated" means altered "by the hand of man" from the natural state. If an "isolated" composition or substance occurs in nature, it has been changed or removed from its original
10 environment, or both. For example, a polynucleotide or a polypeptide naturally present in a living animal is not "isolated," but the same polynucleotide or polypeptide separated from the coexisting materials of its natural state is "isolated", as the term is employed herein.

"Polynucleotide" generally refers to any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. "Polynucleotides" include,
15 without limitation single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, "polynucleotide" refers to triple-stranded regions comprising RNA or DNA or both RNA
20 and DNA. The term polynucleotide also includes DNAs or RNAs containing one or more modified bases and DNAs or RNAs with backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications has been made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically or metabolically modified forms of polynucleotides as typically found
25 in nature, as well as the chemical forms of DNA and RNA characteristic of viruses and cells. "Polynucleotide" also embraces relatively short polynucleotides, often referred to as oligonucleotides.

"Polypeptide" refers to any peptide or protein comprising two or more amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres. "Polypeptide"
30 refers to both short chains, commonly referred to as peptides, oligopeptides or oligomers, and to longer chains, generally referred to as proteins. Polypeptides may contain amino acids other than the 20 gene-encoded amino acids. "Polypeptides" include amino acid sequences modified either by natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more

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detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cystine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York, 1993 and Wold, F., Posttranslational Protein Modifications: Perspectives and Prospects, pgs. 1-12 in POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, 1983; Seifter *et al.*, "Analysis for protein modifications and nonprotein cofactors", *Meth Enzymol* (1990) 182:626-646 and Rattan *et al.*, "Protein Synthesis: Posttranslational Modifications and Aging", *Ann NY Acad Sci* (1992) 663:48-62.

"Variant" as the term is used herein, is a polynucleotide or polypeptide that differs from a reference polynucleotide or polypeptide respectively, but retains essential properties. A typical variant of a polynucleotide differs in nucleotide sequence from another, reference polynucleotide. Changes in the nucleotide sequence of the variant may or may not alter the amino acid sequence of a polypeptide encoded by the reference polynucleotide. Nucleotide changes may result in amino acid substitutions, additions, deletions, fusions and truncations in the polypeptide encoded by the reference sequence, as discussed below. A typical variant of a polypeptide differs in amino acid sequence from another, reference polypeptide. Generally, differences are limited so that the sequences of the reference polypeptide and the variant are closely similar overall and, in many regions, identical. A variant and reference polypeptide may differ in amino acid sequence by one or more substitutions, additions, deletions in any combination. A substituted or inserted amino

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acid residue may or may not be one encoded by the genetic code. A variant of a polynucleotide or polypeptide may be a naturally occurring such as an allelic variant, or it may be a variant that is not known to occur naturally. Non-naturally occurring variants of polynucleotides and polypeptides may be made by mutagenesis techniques or by direct synthesis.

- 5 “Identity” is a measure of the identity of nucleotide sequences or amino acid sequences. In general, the sequences are aligned so that the highest order match is obtained. “Identity” *per se* has an art-recognized meaning and can be calculated using published techniques. See, e.g.: (COMPUTATIONAL MOLECULAR BIOLOGY, Lesk, A.M., ed., Oxford University Press, New York, 1988; BIOCOMPUTING: INFORMATICS AND GENOME PROJECTS, Smith, D.W., ed.,
10 Academic Press, New York, 1993; COMPUTER ANALYSIS OF SEQUENCE DATA, PART I, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey, 1994; SEQUENCE ANALYSIS IN MOLECULAR BIOLOGY, von Heinje, G., Academic Press, 1987; and SEQUENCE ANALYSIS PRIMER, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991). While there exist a number of methods to measure identity between two
15 polynucleotide or polypeptide sequences, the term “identity” is well known to skilled artisans (Carillo, H., and Lipton, D., *SIAM J Applied Math* (1988) 48:1073). Methods commonly employed to determine identity or similarity between two sequences include, but are not limited to, those disclosed in Guide to Huge Computers, Martin J. Bishop, ed., Academic Press, San Diego, 1994, and Carillo, H., and Lipton, D., *SIAM J Applied Math* (1988) 48:1073. Methods to
20 determine identity and similarity are codified in computer programs. Preferred computer program methods to determine identity and similarity between two sequences include, but are not limited to, GCS program package (Devereux, J., *et al.*, *Nucleic Acids Research* (1984) 12(1):387), BLASTP, BLASTN, FASTA (Atschul, S.F. *et al.*, *J Molec Biol* (1990) 215:403).

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Polypeptides of the Invention

In one aspect, the present invention relates to hYAK3 polypeptides. The hYAK3 polypeptides include the polypeptide of SEQ ID NO:2 or 4; as well as polypeptides comprising the amino acid sequence of SEQ ID NO: 2 or 4; and polypeptides comprising the amino acid sequence which have at least 80% identity to that of SEQ ID NO:2 or 4 over its entire length, and still more preferably at least 90% identity, and even still more preferably at least 95% identity to SEQ ID NO: 2 or 4. Also included within hYAK3 polypeptides are polypeptides having the amino acid sequence which have at least 80% identity to the polypeptide having the amino acid sequence of SEQ ID NO:2 or 4 over its entire length, and still more preferably at least 90% identity, and still more preferably at least 95% identity to SEQ ID NO:2 or 4. Preferably hYAK3 polypeptide exhibit at least one biological activity of hYAK3.

The hYAK3 polypeptides may be in the form of the "mature" protein or may be a part of a larger protein such as a fusion protein. It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification such as multiple histidine residues, or an additional sequence for stability during recombinant production.

Biologically active fragments of the hYAK3 polypeptides are also included in the invention. A fragment is a polypeptide having an amino acid sequence that entirely is the same as part, but not all, of the amino acid sequence of the aforementioned hYAK3 polypeptides. As with hYAK3 polypeptides, fragments may be "free-standing," or comprised within a larger polypeptide of which they form a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, and 101 to the end of hYAK3 polypeptide. In this context "about" includes the particularly recited ranges larger or smaller by several, 5, 4, 3, 2 or 1 amino acid at either extreme or at both extremes.

Preferred fragments include, for example, truncation polypeptides having the amino acid sequence of hYAK3 polypeptides, except for deletion of a continuous series of residues that includes the amino terminus, or a continuous series of residues that includes the carboxyl terminus or deletion of two continuous series of residues, one including the amino terminus and one including the carboxyl terminus. Also preferred are fragments characterized by structural or functional attributes such as fragments that comprise alpha-helix and alpha-helix forming regions, beta-sheet and beta-sheet-forming regions, turn and turn-forming regions, coil and coil-forming regions, hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions,

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flexible regions, surface-forming regions, substrate binding region, and high antigenic index regions. Biologically active fragments are those that mediate hYAK3 activity, including those with a similar activity or an improved activity, or with a decreased undesirable activity. Also included are those that are antigenic or immunogenic in an animal, especially in a human.

5 Preferably, all of these polypeptide fragments retain the biological activity of the hYAK3, including antigenic activity. Variants of the defined sequence and fragments also form part of the present invention. Preferred variants are those that vary from the referents by conservative amino acid substitutions -- i.e., those that substitute a residue with another of like characteristics. Typical such substitutions are among Ala, Val, Leu and Ile; among Ser and Thr; among the acidic residues
10 Asp and Glu; among Asn and Gln; and among the basic residues Lys and Arg; or aromatic residues Phe and Tyr. Particularly preferred are variants in which several, 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination.

The hYAK3 polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced
15 polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

Polynucleotides of the Invention

Another aspect of the invention relates to hYAK3 polynucleotides. hYAK3 polynucleotides
20 include isolated polynucleotides which encode the hYAK3 polypeptides and fragments, and polynucleotides closely related thereto. More specifically, hYAK3 polynucleotide of the invention include a polynucleotide comprising the nucleotide sequence set forth in SEQ ID NO:1 or 3 encoding a hYAK3 polypeptide of SEQ ID NO: 2 or 4, and polynucleotide having the particular sequence of SEQ ID NO:1 or 3. hYAK3 polynucleotides further include a polynucleotide
25 comprising a nucleotide sequence that has at least 80% identity to a nucleotide sequence encoding the hYAK3 polypeptide of SEQ ID NO:2 or 4 over its entire length, and a polynucleotide that is at least 80% identical to that having SEQ ID NO:1 or 3 over its entire length. In this regard, polynucleotides at least 90% identical are particularly preferred, and those with at least 95% are especially preferred. Furthermore, those with at least 97% are highly preferred and those with at
30 least 98-99% are most highly preferred, with at least 99% being the most preferred. Also included under hYAK3 polynucleotides are a nucleotide sequence which has sufficient identity to a nucleotide sequence contained in SEQ ID NO:1 or 3 to hybridize under conditions useable for amplification or for use as a probe or marker. The invention also provides polynucleotides which are complementary to such hYAK3 polynucleotides.

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hYAK3 of the invention is structurally related to other proteins of the serine/threonine protein kinase family, as shown by the results of sequencing the cDNA encoding human hYAK3. The cDNA sequence contains an open reading frame encoding a polypeptide of 588/568 (α and β forms, respectively) amino acids. Amino acid of sequence of Figures 1 and 2 (SEQ ID NOS:2 and 4, respectively) has about 65% identity (using FASTA) in 402 amino acid residues with *C. elegans* protein kinase F49E11.1. Furthermore, hYAK3 is 49% identical to *S. pombe* protein kinase SPAC2F7.03c over 315 amino acids (Barrell et al., *Schizosaccharomyces pombe* chromosome I sequencing project, 1995) and 46% identical to *S. cerevisiae* protein kinase YAK1 over 286 amino acids (Garrett and Broach, *Genes & Develop.* 3:1336-1348, 1989). Nucleotide sequence of Figures 1 and 2 (SEQ ID NOS:1 and 4, respectively) has about 64% identity (using FASTA) in 672 nucleotide residues with *C. elegans* protein kinase F49E11.1.

One polynucleotide of the present invention encoding hYAK3 may be obtained using standard cloning and screening, from a cDNA library derived from mRNA in cells of human testis and skeletal muscle using the expressed sequence tag (EST) analysis (Adams, M.D., et al. *Science* (1991) 252:1651-1656; Adams, M.D. et al., *Nature*, (1992) 355:632-634; Adams, M.D., et al., *Nature* (1995) 377 Supp:3-174). Polynucleotides of the invention can also be obtained from natural sources such as genomic DNA libraries or can be synthesized using well known and commercially available techniques.

The nucleotide sequence encoding hYAK3 polypeptide of SEQ ID NO:2 or 4 may be identical over its entire length to the coding sequence set forth in Figure 1 or 2 (SEQ ID NO:1 or 3), or may be a degenerate form of this nucleotide sequence encoding the polypeptide of SEQ ID NO:2 or 4, or may be highly identical to a nucleotide sequence that encodes the polypeptide of SEQ ID NO:2 or 4. Preferably, the polynucleotides of the invention comprise a nucleotide sequence that is highly identical, at least 80% identical, with a nucleotide sequence encoding a hYAK3 polypeptide, or at least 80% identical with the sequence contained in Figure 1 or 2 (SEQ ID NO: 1 or 3) encoding hYAK3 polypeptide, or at least 80% identical to a nucleotide sequence encoding the polypeptide of SEQ ID NO:2 or 4.

When the polynucleotides of the invention are used for the recombinant production of hYAK3 polypeptide, the polynucleotide may include the coding sequence for the mature polypeptide or a fragment thereof, by itself; the coding sequence for the mature polypeptide or fragment in reading frame with other coding sequences, such as those encoding a leader or secretory sequence, a pre-, or pro- or prepro- protein sequence, or other fusion peptide portions. For example, a marker sequence which facilitates purification of the fused polypeptide can be encoded. In certain preferred embodiments of this aspect of the invention, the marker sequence is a hexa-histidine

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peptide, as provided in the pQE vector (Qiagen, Inc.) and described in Gentz *et al.*, *Proc Natl Acad Sci USA* (1989) 86:821-824, or is an HA tag. The polynucleotide may also contain non-coding 5' and 3' sequences, such as transcribed, non-translated sequences, splicing and polyadenylation signals, ribosome binding sites and sequences that stabilize mRNA.

5 Further preferred embodiments are polynucleotides encoding hYAK3 variants comprise the amino acid sequence hYAK3 polypeptide of Figure 1 or 2 (SEQ ID NO:2 or 4) in which several, 5-10, 1-5, 1-3, 1-2 or 1 amino acid residues are substituted, deleted or added, in any combination.

The present invention further relates to polynucleotides that hybridize to the herein above-described sequences. In this regard, the present invention especially relates to polynucleotides which
10 hybridize under stringent conditions to the herein above-described polynucleotides. As herein used, the term "stringent conditions" means hybridization will occur only if there is at least 95% and preferably at least 97% identity between the sequences.

Polynucleotides of the invention, which are identical or sufficiently identical to a nucleotide sequence contained in SEQ ID NO:1 or 3, may be used as hybridization probes for cDNA and
15 genomic DNA, to isolate full-length cDNAs and genomic clones encoding hYAK3 polypeptide and to isolate cDNA and genomic clones of other genes that have a high sequence similarity to the hYAK3 gene. Such hybridization techniques are known to those of skill in the art. Typically these nucleotide sequences are 70% identical, preferably 80% identical, more preferably 90% identical to that of the referent. The probes generally will comprise at least 15 nucleotides. Preferably, such
20 probes will have at least 30 nucleotides and may have at least 50 nucleotides. Particularly preferred probes will range between 30 and 50 nucleotides.

In one embodiment, to obtain a polynucleotide encoding hYAK3 comprises the steps of screening an appropriate library under stringent hybridization conditions with a labeled probe having the SEQ ID NO: 1 or 3 or a fragment thereof; and isolating full-length cDNA and genomic clones
25 containing said polynucleotide sequence. Such hybridization techniques are well known to those of skill in the art. Stringent hybridization conditions are as defined above or alternatively conditions under overnight incubation at 42°C in a solution comprising: 50% formamide, 5xSSC (150mM NaCl, 15mM trisodium citrate), 50 mM sodium phosphate (pH7.6), 5x Denhardt's solution, 10 % dextran sulfate, and 20 microgram/ml denatured, sheared salmon sperm DNA, followed by washing
30 the filters in 0.1x SSC at about 65°C.

The polynucleotides and polypeptides of the present invention may be employed as research reagents and materials for discovery of treatments and diagnostics to animal and human disease.

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Vectors, Host Cells, Expression

The present invention also relates to vectors which comprise a polynucleotide or polynucleotides of the present invention, and host cells which are genetically engineered with vectors of the invention and to the production of polypeptides of the invention by recombinant techniques.

- 5 Cell-free translation systems can also be employed to produce such proteins using RNAs derived from the DNA constructs of the present invention.

For recombinant production, host cells can be genetically engineered to incorporate expression systems or portions thereof for polynucleotides of the present invention. Introduction of polynucleotides into host cells can be effected by methods described in many standard laboratory
10 manuals, such as Davis et al., *BASIC METHODS IN MOLECULAR BIOLOGY* (1986) and Sambrook et al., *MOLECULAR CLONING: A LABORATORY MANUAL*, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989) such as calcium phosphate transfection, DEAE-dextran mediated transfection, transvection, microinjection, cationic lipid-mediated transfection, electroporation, transduction, scrape loading, ballistic introduction or infection.

- 15 Representative examples of appropriate hosts include bacterial cells, such as streptococci, staphylococci, *E. coli*, *Streptomyces* and *Bacillus subtilis* cells; fungal cells, such as yeast cells and *Aspergillus* cells; insect cells such as *Drosophila* S2 and *Spodoptera* Sf9 cells; animal cells such as CHO, COS, HeLa, C127, 3T3, BHK, 293 and Bowes melanoma cells; and plant cells.

- A great variety of expression systems can be used. Such systems include, among others,
20 chromosomal, episomal and virus-derived systems, e.g., vectors derived from bacterial plasmids, from bacteriophage, from transposons, from yeast episomes, from insertion elements, from yeast chromosomal elements, from viruses such as baculoviruses, papova viruses, such as SV40, vaccinia viruses, adenoviruses, fowl pox viruses, pseudorabies viruses and retroviruses, and vectors derived from combinations thereof, such as those derived from plasmid and bacteriophage genetic elements,
25 such as cosmids and phagemids. The expression systems may contain control regions that regulate as well as engender expression. Generally, any system or vector suitable to maintain, propagate or express polynucleotides to produce a polypeptide in a host may be used. The appropriate nucleotide sequence may be inserted into an expression system by any of a variety of well-known and routine techniques, such as, for example, those set forth in Sambrook et al., *MOLECULAR CLONING, A*
30 *LABORATORY MANUAL* (*supra*).

For secretion of the translated protein into the lumen of the endoplasmic reticulum, into the periplasmic space or into the extracellular environment, appropriate secretion signals may be incorporated into the desired polypeptide. These signals may be endogenous to the polypeptide or they may be heterologous signals.

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If the hYAK3 polypeptide is to be expressed for use in screening assays, generally, it is preferred that the polypeptide be produced at the surface of the cell. In this event, the cells may be harvested prior to use in the screening assay. If hYAK3 polypeptide is secreted into the medium, the medium can be recovered in order to recover and purify the polypeptide; if produced intracellularly, the cells must first be lysed before the polypeptide is recovered. hYAK3 polypeptides can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography is employed for purification. Well known techniques for refolding proteins may be employed to regenerate active conformation when the polypeptide is denatured during isolation and or purification.

Diagnostic Assays

This invention also relates to the use of hYAK3 polynucleotides for use as diagnostic reagents. Detection of a mutated form of hYAK3 gene associated with a dysfunction will provide a diagnostic tool that can add to or define a diagnosis of a disease or susceptibility to a disease which results from under-expression, over-expression or altered expression of hYAK3. Individuals carrying mutations in the hYAK3 gene may be detected at the DNA level by a variety of techniques. Nucleic acids for diagnosis may be obtained from a subject's cells, such as from blood, urine, saliva, tissue biopsy or autopsy material. The genomic DNA may be used directly for detection or may be amplified enzymatically by using PCR or other amplification techniques prior to analysis. RNA or cDNA may also be used in similar fashion. Deletions and insertions can be detected by a change in size of the amplified product in comparison to the normal genotype. Point mutations can be identified by hybridizing amplified DNA to labeled hYAK3 nucleotide sequences. Perfectly matched sequences can be distinguished from mismatched duplexes by RNase digestion or by differences in melting temperatures. DNA sequence differences may also be detected by alterations in electrophoretic mobility of DNA fragments in gels, with or without denaturing agents, or by direct DNA sequencing. See, e.g., Myers *et al.*, *Science* (1985) 230:1242. Sequence changes at specific locations may also be revealed by nuclease protection assays, such as RNase and S1 protection or the chemical cleavage method. See Cotton *et al.*, *Proc Natl Acad Sci USA* (1985) 85: 4397-4401. In another embodiment, an array of oligonucleotide probes comprising hYAK3 nucleotide sequence or fragments thereof can be constructed to conduct efficient screening of e.g., genetic mutations. Array technology methods are well known and have general applicability and can be used to

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address a variety of questions in molecular genetics including gene expression, genetic linkage, and genetic variability. (See for example: M.Chee et al., Science, Vol 274, pp 610-613 (1996)).

The diagnostic assays offer a process for diagnosing or determining a susceptibility to bone loss including osteoporosis; inflammatory diseases such as Adult Respiratory Disease Syndrome (ARDS), Rheumatoid arthritis, Osteoarthritis, Inflammatory Bowel Disease (IBD), psoriasis, dermatitis, asthma, allergies; infections such as bacterial, fungal, protozoan and viral infections, particularly infections caused by HIV-1 or HIV-2; HIV-associated cachexia and other immunodeficiency disorders; septic shock; pain; injury; cancers including testicular cancer; anorexia; bulimia; Parkinson's disease; cardiovascular disease including restenosis, atherosclerosis, acute heart failure, myocardial infarction; hypotension; hypertension; urinary retention; angina pectoris; ulcers; benign prostatic hypertrophy; and psychotic and neurological disorders, including anxiety, schizophrenia, manic depression, delirium, dementia, severe mental retardation and dyskinesias, such as Huntington's disease or Gilles de la Tourette's syndrome. through detection of mutation in the hYAK3 gene by the methods described.

In addition, bone loss including osteoporosis; inflammatory diseases such as Adult Respiratory Disease Syndrome (ARDS), Rheumatoid arthritis, Osteoarthritis, Inflammatory Bowel Disease (IBD), psoriasis, dermatitis, asthma, allergies; infections such as bacterial, fungal, protozoan and viral infections, particularly infections caused by HIV-1 or HIV-2; HIV-associated cachexia and other immunodeficiency disorders; septic shock; pain; injury; cancers including testicular cancer; anorexia; bulimia; Parkinson's disease; cardiovascular disease including restenosis, atherosclerosis, acute heart failure, myocardial infarction; hypotension; hypertension; urinary retention; angina pectoris; ulcers; benign prostatic hypertrophy; and psychotic and neurological disorders, including anxiety, schizophrenia, manic depression, delirium, dementia, severe mental retardation and dyskinesias, such as Huntington's disease or Gilles de la Tourette's syndrome., can be diagnosed by methods comprising determining from a sample derived from a subject an abnormally decreased or increased level of hYAK3 polypeptide or hYAK3 mRNA. Decreased or increased expression can be measured at the RNA level using any of the methods well known in the art for the quantitation of polynucleotides, such as, for example, PCR, RT-PCR, RNase protection, Northern blotting and other hybridization methods. Assay techniques that can be used to determine levels of a protein, such as an hYAK3 polypeptide, in a sample derived from a host are well-known to those of skill in the art. Such assay methods include radioimmunoassays, competitive-binding assays, Western Blot analysis and ELISA assays.

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Chromosome Assays

The nucleotide sequences of the present invention are also valuable for chromosome identification. The sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome. The mapping of relevant sequences to chromosomes

5 according to the present invention is an important first step in correlating those sequences with gene associated disease. Once a sequence has been mapped to a precise chromosomal location, the physical position of the sequence on the chromosome can be correlated with genetic map data. Such data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library). The relationship between genes and

10 diseases that have been mapped to the same chromosomal region are then identified through linkage analysis (coinheritance of physically adjacent genes).

The differences in the cDNA or genomic sequence between affected and unaffected individuals can also be determined. If a mutation is observed in some or all of the affected individuals but not in any normal individuals, then the mutation is likely to be the causative agent

15 of the disease.

Antibodies

The polypeptides of the invention or their fragments or analogs thereof, or cells expressing them can also be used as immunogens to produce antibodies immunospecific for the hYAK3

20 polypeptides. The term "immunospecific" means that the antibodies have substantially greater affinity for the polypeptides of the invention than their affinity for other related polypeptides in the prior art.

Antibodies generated against the hYAK3 polypeptides can be obtained by administering the polypeptides or epitope-bearing fragments, analogs or cells to an animal, preferably a nonhuman,

25 using routine protocols. For preparation of monoclonal antibodies, any technique which provides antibodies produced by continuous cell line cultures can be used. Examples include the hybridoma technique (Kohler, G. and Milstein, C., *Nature* (1975) 256:495-497), the trioma technique, the human B-cell hybridoma technique (Kozbor *et al.*, *Immunology Today* (1983) 4:72) and the EBV-hybridoma technique (Cole *et al.*, MONOCLONAL ANTIBODIES AND CANCER THERAPY, pp.

30 77-96, Alan R. Liss, Inc., 1985).

Techniques for the production of single chain antibodies (U.S. Patent No. 4,946,778) can also be adapted to produce single chain antibodies to polypeptides of this invention. Also, transgenic mice, or other organisms including other mammals, may be used to express humanized antibodies.

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The above-described antibodies may be employed to isolate or to identify clones expressing the polypeptide or to purify the polypeptides by affinity chromatography.

Antibodies against hYAK3 polypeptides may also be employed to treat bone loss including osteoporosis; inflammatory diseases such as Adult Respiratory Disease Syndrome (ARDS),
 5 Rheumatoid arthritis, Osteoarthritis, Inflammatory Bowel Disease (IBD), psoriasis, dermatitis, asthma, allergies; infections such as bacterial, fungal, protozoan and viral infections, particularly infections caused by HIV-1 or HIV-2; HIV-associated cachexia and other immunodeficiency disorders; septic shock; pain; injury; cancers including testicular cancer; anorexia; bulimia; Parkinson's disease; cardiovascular disease including restenosis, atherosclerosis, acute heart failure,
 10 myocardial infarction; hypotension; hypertension; urinary retention; angina pectoris; ulcers; benign prostatic hypertrophy; and psychotic and neurological disorders, including anxiety, schizophrenia, manic depression, delirium, dementia, severe mental retardation and dyskinesias, such as Huntington's disease or Gilles de la Tourette's syndrome., among others.

15 Vaccines

Another aspect of the invention relates to a method for inducing an immunological response in a mammal which comprises inoculating the mammal with hYAK3 polypeptide, or a fragment thereof, adequate to produce antibody and/or T cell immune response to protect said animal from bone loss including osteoporosis; inflammatory diseases such as Adult Respiratory
 20 Disease Syndrome (ARDS), Rheumatoid arthritis, Osteoarthritis, Inflammatory Bowel Disease (IBD), psoriasis, dermatitis, asthma, allergies; infections such as bacterial, fungal, protozoan and viral infections, particularly infections caused by HIV-1 or HIV-2; HIV-associated cachexia and other immunodeficiency disorders; septic shock; pain; injury; cancers including testicular cancer; anorexia; bulimia; Parkinson's disease; cardiovascular disease including restenosis, atherosclerosis,
 25 acute heart failure, myocardial infarction; hypotension; hypertension; urinary retention; angina pectoris; ulcers; benign prostatic hypertrophy; and psychotic and neurological disorders, including anxiety, schizophrenia, manic depression, delirium, dementia, severe mental retardation and dyskinesias, such as Huntington's disease or Gilles de la Tourette's syndrome., among others. Yet another aspect of the invention relates to a method of inducing immunological response in a
 30 mammal which comprises, delivering hYAK3 polypeptide via a vector directing expression of hYAK3 polynucleotide *in vivo* in order to induce such an immunological response to produce antibody to protect said animal from diseases.

Further aspect of the invention relates to an immunological/vaccine formulation (composition) which, when introduced into a mammalian host, induces an immunological

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response in that mammal to a hYAK3 polypeptide wherein the composition comprises a hYAK3 polypeptide or hYAK3 gene. The vaccine formulation may further comprise a suitable carrier. Since hYAK3 polypeptide may be broken down in the stomach, it is preferably administered parenterally (including subcutaneous, intramuscular, intravenous, intradermal etc. injection).

5 Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents or thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampoules and vials

10 and may be stored in a freeze-dried condition requiring only the addition of the sterile liquid carrier immediately prior to use. The vaccine formulation may also include adjuvant systems for enhancing the immunogenicity of the formulation, such as oil-in water systems and other systems known in the art. The dosage will depend on the specific activity of the vaccine and can be readily determined by routine experimentation.

15

Screening Assays

The hYAK3 polypeptide of the present invention may be employed in a screening process for compounds which activate (agonists) or inhibit activation of (antagonists, or otherwise called inhibitors) the hYAK3 polypeptide of the present invention. Thus, polypeptides of the invention

20 may also be used to assess identify agonist or antagonists from, for example, cells, cell-free preparations, chemical libraries, and natural product mixtures. These agonists or antagonists may be natural substrates, ligands, receptors, etc., as the case may be, of the polypeptide of the present invention; or may be structural or functional mimetics of the polypeptide of the present invention. See Coligan *et al.*, *Current Protocols in Immunology* 1(2):Chapter 5 (1991).

25

hYAK3 polypeptides are ubiquitous in the mammalian host and are responsible for many biological functions, including many pathologies. Accordingly, it is desirable to find compounds and drugs which stimulate hYAK3 polypeptide on the one hand and which can inhibit the function of hYAK3 polypeptide on the other hand. In general, agonists are employed for therapeutic and prophylactic purposes for such conditions as bone loss including osteoporosis; inflammatory diseases

30 such as Adult Respiratory Disease Syndrome (ARDS), Rheumatoid arthritis, Osteoarthritis, Inflammatory Bowel Disease (IBD), psoriasis, dermatitis, asthma, allergies; infections such as bacterial, fungal, protozoan and viral infections, particularly infections caused by HIV-1 or HIV-2; HIV-associated cachexia and other immunodeficiency disorders; septic shock; pain; injury; cancers including testicular cancer; anorexia; bulimia; Parkinson's disease; cardiovascular disease including

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restenosis, atherosclerosis, acute heart failure, myocardial infarction; hypotension; hypertension; urinary retention; angina pectoris; ulcers; benign prostatic hypertrophy; and psychotic and neurological disorders, including anxiety, schizophrenia, manic depression, delirium, dementia, severe mental retardation and dyskinesias, such as Huntington's disease or Gilles de la Tourette's syndrome.. Antagonists may be employed for a variety of therapeutic and prophylactic purposes for such conditions as bone loss including osteoporosis; inflammatory diseases such as Adult Respiratory Disease Syndrome (ARDS), Rheumatoid arthritis, Osteoarthritis, Inflammatory Bowel Disease (IBD), psoriasis, dermatitis, asthma, allergies; infections such as bacterial, fungal, protozoan and viral infections, particularly infections caused by HIV-1 or HIV-2; HIV-associated cachexia and other immunodeficiency disorders; septic shock; pain; injury; cancers including testicular cancer; anorexia; bulimia; Parkinson's disease; cardiovascular disease including restenosis, atherosclerosis, acute heart failure, myocardial infarction; hypotension; hypertension; urinary retention; angina pectoris; ulcers; benign prostatic hypertrophy; and psychotic and neurological disorders, including anxiety, schizophrenia, manic depression, delirium, dementia, severe mental retardation and dyskinesias, such as Huntington's disease or Gilles de la Tourette's syndrome..

In general, such screening procedures may involve using appropriate cells which express the hYAK3 polypeptide or respond to hYAK3 polypeptide of the present invention. Such cells include cells from mammals, yeast, *Drosophila* or *E. coli*. Cells which express the hYAK3 polypeptide (or cell membrane containing the expressed polypeptide) or respond to hYAK3 polypeptide are then contacted with a test compound to observe binding, or stimulation or inhibition of a functional response. The ability of the cells which were contacted with the candidate compounds is compared with the same cells which were not contacted for hYAK3 activity.

The knowledge that the hYAK3 encodes a protein kinase suggests that recombinant forms can be used to establish a protein kinase activity. Typically this would involve the direct incubation of hYAK3 with a protein or peptide substrate in the presence of γ -³²P-ATP, followed by the measurement of radioactivity incorporated into the substrate by separation and counting. Separation methods include immunoprecipitation, conjugation of substrate to a bead allowing separation by centrifugation or determination of incorporation by scintillation proximity assay, SDS-PAGE followed by autoradiography or biosensor analysis. While the specific substrates are not yet known, candidates include hYAK3 itself (autophosphorylation), myelin basic protein, casein, histone and HSP27. Other substances might be discovered by incubating hYAK3 with random peptides conjugated to solid supports or displayed on the surface of phage or by incubation of hYAK3 with mammalian cell lysates and γ -³²P-ATP, followed by separation of the labelled target proteins, and sequencing. The protein kinase activity of hYAK3 may require incubation with a specific upstream

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effector. This may be achieved by preincubating hYAK3 with lysates from a variety of stimulated eukaryotic cells and ATP. These assays permit the discovery and modification of compounds which inhibit hYAK3 kinase activity *in vitro* and would be expected to have effects on proliferation of osteoblasts, chondrocytes, cardiac myocytes or skeletal myoblasts. Any inhibitors so identified
5 would be expected to have up-regulatory effects on proliferation and be useful as a therapeutic for the treatment and prevention of diseases such as osteoporosis, osteoarthritis, cardiomyopathy and cachexia.

This invention contemplates the treatment and/ or amelioration of such diseases by administering an hYAK3 inhibiting amount of a compound. Without wishing to be bound by any
10 particular theory of the functioning of the hYAK3 of this invention, it is believed that among the useful inhibitors of hYAK3 function are those compounds which inhibit the kinase activity of the hYAK3. Other sites of inhibition are, of course, possible owing to its position in a signal transduction cascade. Therefore, inhibiting the interaction of hYAK3 with one or more of its upstream or downstream modulators/substrates is also contemplated by this invention. Inhibitors of
15 protein-protein interactions between hYAK3 and other factors could lead to the development of pharmaceutical agents for the modulation of hYAK3 activity.

The assays may simply test binding of a candidate compound wherein adherence to the cells bearing the hYAK3 polypeptide is detected by means of a label directly or indirectly associated with the candidate compound or in an assay involving competition with a labeled
20 competitor. Further, these assays may test whether the candidate compound results in a signal generated by activation of the hYAK3 polypeptide, using detection systems appropriate to the cells bearing the hYAK3 polypeptide. Inhibitors of activation are generally assayed in the presence of a known agonist and the effect on activation by the agonist by the presence of the candidate compound is observed. Standard methods for conducting such screening assays are well
25 understood in the art.

Examples of potential hYAK3 polypeptide antagonists include antibodies or, in some cases, oligonucleotides or proteins which are closely related to the ligands, substrates, receptors, etc., as the case may be, of the hYAK3 polypeptide, e.g., a fragment of the ligands, substrates, receptors, or small molecules which bind to the polypeptide of the present invention but do not elicit a response, so
30 that the activity of the polypeptide is prevented.

Prophylactic and Therapeutic Methods

This invention provides methods of treating an abnormal conditions related to both an excess of and insufficient amounts of hYAK3 polypeptide activity.

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If the activity of hYAK3 polypeptide is in excess, several approaches are available. One approach comprises administering to a subject an inhibitor compound (antagonist) as hereinabove described along with a pharmaceutically acceptable carrier in an amount effective to inhibit activation by blocking binding of ligands to the hYAK3 polypeptide, or by inhibiting a second
 5 signal, and thereby alleviating the abnormal condition.

In another approach, soluble forms of hYAK3 polypeptides still capable of binding the ligand in competition with endogenous hYAK3 polypeptide may be administered. Typical embodiments of such competitors comprise fragments of the hYAK3 polypeptide.

In still another approach, expression of the gene encoding endogenous hYAK3
 10 polypeptide can be inhibited using expression blocking techniques. Known such techniques involve the use of antisense sequences, either internally generated or separately administered. See, for example, O'Connor, *J Neurochem* (1991) 56:560 in Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Alternatively, oligonucleotides which form triple helices with the gene can be supplied. See, for example, Lee *et al.*, *Nucleic Acids Res* (1979) 6:3073; Cooney *et al.*, *Science* (1988) 241:456; Dervan *et al.*,
 15 *Science* (1991) 251:1360. These oligomers can be administered *per se* or the relevant oligomers can be expressed *in vivo*.

For treating abnormal conditions related to an under-expression of hYAK3 and its activity, several approaches are also available. One approach comprises administering to a subject a
 20 therapeutically effective amount of a compound which activates hYAK3 polypeptide, i.e., an agonist as described above, in combination with a pharmaceutically acceptable carrier, to thereby alleviate the abnormal condition. Alternatively, gene therapy may be employed to effect the endogenous production of hYAK3 by the relevant cells in the subject. For example, a polynucleotide of the invention may be engineered for expression in a replication defective retroviral vector, as discussed
 25 above. The retroviral expression construct may then be isolated and introduced into a packaging cell transduced with a retroviral plasmid vector containing RNA encoding a polypeptide of the present invention such that the packaging cell now produces infectious viral particles containing the gene of interest. These producer cells may be administered to a subject for engineering cells *in vivo* and expression of the polypeptide *in vivo*. For overview of gene therapy, see Chapter 20, *Gene Therapy and other Molecular Genetic-based Therapeutic Approaches*, (and references cited therein) in
 30 Human Molecular Genetics, T Strachan and A P Read, BIOS Scientific Publishers Ltd (1996).

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Formulation and Administration

Peptides, such as the soluble form of hYAK3 polypeptides, and agonists and antagonist peptides or small molecules, may be formulated in combination with a suitable pharmaceutical carrier. Such formulations comprise a therapeutically effective amount of the polypeptide or compound, and a pharmaceutically acceptable carrier or excipient. Such carriers include but are not limited to, saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof. Formulation should suit the mode of administration, and is well within the skill of the art. The invention further relates to pharmaceutical packs and kits comprising one or more containers filled with one or more of the ingredients of the aforementioned compositions of the invention.

Polypeptides and other compounds of the present invention may be employed alone or in conjunction with other compounds, such as therapeutic compounds.

Preferred forms of systemic administration of the pharmaceutical compositions include injection, typically by intravenous injection. Other injection routes, such as subcutaneous, intramuscular, or intraperitoneal, can be used. Alternative means for systemic administration include transmucosal and transdermal administration using penetrants such as bile salts or fusidic acids or other detergents. In addition, if properly formulated in enteric or encapsulated formulations, oral administration may also be possible. Administration of these compounds may also be topical and/or localized, in the form of salves, pastes, gels and the like.

The dosage range required depends on the choice of peptide, the route of administration, the nature of the formulation, the nature of the subject's condition, and the judgment of the attending practitioner. Suitable dosages, however, are in the range of 0.1-100 $\mu\text{g/kg}$ of subject. Wide variations in the needed dosage, however, are to be expected in view of the variety of compounds available and the differing efficiencies of various routes of administration. For example, oral administration would be expected to require higher dosages than administration by intravenous injection. Variations in these dosage levels can be adjusted using standard empirical routines for optimization, as is well understood in the art.

Polypeptides used in treatment can also be generated endogenously in the subject, in treatment modalities often referred to as "gene therapy" as described above. Thus, for example, cells from a subject may be engineered with a polynucleotide, such as a DNA or RNA, to encode a polypeptide *ex vivo*, and for example, by the use of a retroviral plasmid vector. The cells are then introduced into the subject.

Examples

The examples below are carried out using standard techniques, which are well known and routine to those of skill in the art, except where otherwise described in detail. The examples illustrate, but do not limit the invention.

5 Example 1

A partial clone was initially identified through random searches of the Human Genome Sciences database. This partial clone (~ 1kb) showed significant homology to YAK1 from *S. cerevisiae*. To obtain the full length cDNA: Using the insert of the above partial clone as a probe,
10 1M plaques were screened from both a human testis and skeletal muscle cDNA library (Stratagene, LaJolla CA). Library screening procedure is described by (Elgin, et al. Strategies 4: 8-9, 1991). The probes were α -³²P labeled, using a Random Primed Labeling Kit (Boehringer Mannheim, Germany, Cat. # 1585584) and purified by running over Sephadex^{*} G-50 columns (Pharmacia Biotech. Cat. # 17-0855-02). The hybridization and washing conditions were according to J. Sambrook, E.F. Fritch and T. Maniatis (1989) A Laboratory Manual Second. Ed. Vol. 1 pp. 2.69-2.81 Cold Spring
15 Harbor Laboratory Press, Cold Spring Harbor, New York). Several positive clones were isolated from each library by plaque purification and fragments containing the inserts were excised and sequenced. The longest insert obtained from the skeletal muscle and testis libraries was 2.1 kb and 2.3 kb, respectively (SEQ ID NOS:1 and 3, respectively). The presence of an in-frame stop codon
20 immediately 5' of an initiation codon indicated that both cDNA's were full length. Comparison of these two cDNAs indicates that the 3' most 1844 nucleotides are identical. The skeletal muscle cDNA (hYAK3 α) is 266 nucleotides shorter than the testis cDNA (hYAK3 β); however, the skeletal muscle cDNA is 20 amino acids longer at the amino terminus than that obtained from the testis library. The presence of the splice site consensus sequence, AGG, suggests that the differences
25 between these two cDNAs may be due to alternative splicing. Fasta analysis show both peptides to have high homology to a putative serine/threonine kinase of unknown function from *C. elegans* (F49E11.1).

Example 2

30 Northern analysis was carried out to determine the distribution of hYAK3 mRNA in human tissues. The original partial clone was radiolabelled with [³²P]-dATP using a randomly primed labelling kit. Membranes containing mRNA from multiple human tissues (Clontech #7760-1 and #7759-1)) were hybridized with the probe and washed under high stringency conditions as directed. Hybridized mRNA was visualized by exposing the membranes to X-ray film. One major transcript at ~2.3 kb was present in testis. The transcript was not visible in

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any other tissues; however, dot blot analysis using a Human Master blot (Clontech #7770-1) indicated that hYAK3 is expressed in other tissues including skeletal muscle.

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SEQUENCE LISTING

(1) GENERAL INFORMATION

(i) APPLICANTS: Creasy, Caretha AND WEI XIE

(ii) TITLE OF THE INVENTION: Human Protein Kinases hYA
K3

(iii) NUMBER OF SEQUENCES: 4

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(v) COMPUTER READABLE FORM:

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(B) COMPUTER: IBM Compatible
(C) OPERATING SYSTEM: DOS
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(ix) TELECOMMUNICATION INFORMATION:

- (A) TELEPHONE: 610-270-5219
- (B) TELEFAX: 610-270-4026
- (C) TELEX:

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2061 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

```

GGAGCGAAAT GCGCTGAGCT GCAGTGTCTG GTCGAGAGTA CCCGTGGGAG CGTCGCGCCG      60
CGGAGGCAGC CGTCCCGGCG TAGGTGGCGT GGCCGACCGG ACCCCCAACT GGCGCCTCTC      120
CCCGCGCGGG GTCCCGAGCT AGGAGATGGG AGGCACAGCT CGTGGGCCTG GGCGGAAGGA      180
TGCGGGGCCG CCTGGGGCCG GGCTCCCGCC CCAGCAGCGG AGGTTGGGGG ATGGTGTCTA      240
TGACACCTTC ATGATGATAG ATGAAACCAA ATGTCCCCCC TGTTCAAATG TACTCTGCAA      300
TCCTTCTGAA CCACCTCCAC CCAGAAGACT AAATATGACC ACTGAGCAGT TTACAGGAGA      360
TCATACTCAG CACTTTTTTG ATGGAGGTGA GATGAAGGTA GAACAGCTGT TTCAAGAATT      420
TGGCAACAGA AAATCCAATA CTATTCAGTC AGATGGCATC AGTGACTCTG AAAAATGCTC      480
TCCTACTGTT TCTCAGGGTA AAAGTTCAGA TTGCTTGAAT ACAGTAAAAT CCAACAGTTC      540
ATCCAAGGCA CCCAAAGTGG TGCCTCTGAC TCCAGAACAA GCCCTGAAGC AATATAAACA      600
CCACCTCACT GCCTATGAGA AACTGGAAAT AATTAATTAT CCAGAAATTT ACTTTGTAGG      660
TCCAAATGCC AAGAAAAGAC ATGGAGTTAT TGGTGGTCCC AATAATGGAG GGTATGATGA      720
TGCAGATGGG GCCTATATTC ATGTACCTCG AGACCATCTA GCTTATCGAT ATGAGGTGCT      780
GAAAATTATT GGCAAGGGGA GTTTTGGGCA GGTGGCCAGG GTCTATGATC ACAAACCTCG      840
ACAGTACGTG GCCCTAAAAA TGGTGCGCAA TGAGAAGCGC TTTCATCGTC AAGCAGCTGA      900
GGAGATCCGG ATTTTGGAGC ATCTTAAGAA ACAGGATAAA ACTGGTAGTA TGAACGTTAT      960
CCACATGCTG GAAAGTTTCA CATTCGGGAA CCATGTTTGC ATGGCCTTTG AATTGCTGAG     1020
CATAGACCTT TATGAGCTGA TTAAAAAAA TAAGTTTCAG GGTTTTAGCG TCCAGTTGGT     1080
ACGCAAGTTT GCCCAGTCCA TCTTGCAATC TTTGGATGCC CTCCACAAAA ATAAGATTAT     1140
TCACTGCGAT CTGAAGCCAG AAAACATTCT CCTGAAACAC CACGGGCGCA GTTCAACCAA     1200
GGTCATTGAC TTTGGGTCCA GCTGTTTCGA GTACCAGAAG CTCTACACAT ATATCCAGTC     1260
TCGGTTCTAC AGAGCTCCAG AAATCATCTT AGGAAGCCGC TACAGCACAC CAATTGACAT     1320
ATGGAGTTTT GGCTGCATCC TTGCAGAACT TTTAACAGGA CAGCCTCTCT TCCCTGGAGA     1380
GGATGAAGGA GACCAGTTGG CCTCCATGAT GGAGCTTCTA GGGATGCCAC CACCAAAACT     1440

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TCTGGAGCAA TCCAAACGTG CCAAGTACTT TATTAATTCC AAGGGCATAC CCCGCTACTG 1500
CTCTGTGACT ACCCAGGCAG ATGGGAGGGT TGTGCTTG TG GGGGTCGCT CACGTAGGGG 1560
TAAAAAGCGG GGTCCCCCAG GCAGCAAAGA CTGGGGGACA GCACTGAAAG GGTGTGATGA 1620
CTACTTGTTT ATAGAGTTCT TGAAAAGGTG TCTTCACTGG GACCCCTCTG CCCGCTTGAC 1680
CCCAGCTCAA GCATTAAGAC ACCCTTGGAT TAGCAAGTCT GTCCCCAGAC CTCTCACCAC 1740
CATAGACAAG GTGTCAGGGA AACGGGTAGT TAATCCTGCA AGTGCTTTCC AGGGATTGGG 1800
TTCTAAGCTG CCTCCAGTTG TTGGAATAGC CAATAAGCTT AAAGCTAACT TAATGTCAGA 1860
AACCAATGGT AGTATACCCC TATGCAGTGT ATTGCCAAAA CTGATTAGCT AGTGGACAGA 1920
GATATGCCCA GAGATGCATA TGTGTATATT TTTATGATCT TACAAACCTG CAAATGGAAA 1980
AAATGCAAGC CCATTGGTGG ATGTTTTTGT TAGAGTAGAC TTTTTTTAAA CAAGACAAAA 2040
CATTTTTATA TGATTATAAA A 2061

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(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 588 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```

Met Gly Gly Thr Ala Arg Gly Pro Gly Arg Lys Asp Ala Gly Pro Pro
 1             5             10             15
Gly Ala Gly Leu Pro Pro Gln Gln Arg Arg Leu Gly Asp Gly Val Tyr
      20             25             30
Asp Thr Phe Met Met Ile Asp Glu Thr Lys Cys Pro Pro Cys Ser Asn
      35             40             45
Val Leu Cys Asn Pro Ser Glu Pro Pro Pro Pro Arg Arg Leu Asn Met
      50             55             60
Thr Thr Glu Gln Phe Thr Gly Asp His Thr Gln His Phe Leu Asp Gly
65             70             75             80
Gly Glu Met Lys Val Glu Gln Leu Phe Gln Glu Phe Gly Asn Arg Lys
      85             90             95
Ser Asn Thr Ile Gln Ser Asp Gly Ile Ser Asp Ser Glu Lys Cys Ser
      100            105            110
Pro Thr Val Ser Gln Gly Lys Ser Ser Asp Cys Leu Asn Thr Val Lys
      115            120            125
Ser Asn Ser Ser Ser Lys Ala Pro Lys Val Val Pro Leu Thr Pro Glu
      130            135            140
Gln Ala Leu Lys Gln Tyr Lys His His Leu Thr Ala Tyr Glu Lys Leu

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145		150		155		160									
Glu	Ile	Ile	Asn	Tyr	Pro	Glu	Ile	Tyr	Phe	Val	Gly	Pro	Asn	Ala	Lys
		165		170		175									
Lys	Arg	His	Gly	Val	Ile	Gly	Gly	Pro	Asn	Asn	Gly	Gly	Tyr	Asp	Asp
		180		185		190									
Ala	Asp	Gly	Ala	Tyr	Ile	His	Val	Pro	Arg	Asp	His	Leu	Ala	Tyr	Arg
	195			200		205									
Tyr	Glu	Val	Leu	Lys	Ile	Ile	Gly	Lys	Gly	Ser	Phe	Gly	Gln	Val	Ala
	210			215		220									
Arg	Val	Tyr	Asp	His	Lys	Leu	Arg	Gln	Tyr	Val	Ala	Leu	Lys	Met	Val
225		230		235		240									
Arg	Asn	Glu	Lys	Arg	Phe	His	Arg	Gln	Ala	Ala	Glu	Glu	Ile	Arg	Ile
		245		250		255									
Leu	Glu	His	Leu	Lys	Lys	Gln	Asp	Lys	Thr	Gly	Ser	Met	Asn	Val	Ile
		260		265		270									
His	Met	Leu	Glu	Ser	Phe	Thr	Phe	Arg	Asn	His	Val	Cys	Met	Ala	Phe
	275			280		285									
Glu	Leu	Leu	Ser	Ile	Asp	Leu	Tyr	Glu	Leu	Ile	Lys	Lys	Asn	Lys	Phe
	290			295		300									
Gln	Gly	Phe	Ser	Val	Gln	Leu	Val	Arg	Lys	Phe	Ala	Gln	Ser	Ile	Leu
305		310		315		320									
Gln	Ser	Leu	Asp	Ala	Leu	His	Lys	Asn	Lys	Ile	Ile	His	Cys	Asp	Leu
		325		330		335									
Lys	Pro	Glu	Asn	Ile	Leu	Leu	Lys	His	His	Gly	Arg	Ser	Ser	Thr	Lys
		340		345		350									
Val	Ile	Asp	Phe	Gly	Ser	Ser	Cys	Phe	Glu	Tyr	Gln	Lys	Leu	Tyr	Thr
	355			360		365									
Tyr	Ile	Gln	Ser	Arg	Phe	Tyr	Arg	Ala	Pro	Glu	Ile	Ile	Leu	Gly	Ser
	370			375		380									
Arg	Tyr	Ser	Thr	Pro	Ile	Asp	Ile	Trp	Ser	Phe	Gly	Cys	Ile	Leu	Ala
385		390		395		400									
Glu	Leu	Leu	Thr	Gly	Gln	Pro	Leu	Phe	Pro	Gly	Glu	Asp	Glu	Gly	Asp
		405		410		415									
Gln	Leu	Ala	Ser	Met	Met	Glu	Leu	Leu	Gly	Met	Pro	Pro	Pro	Lys	Leu
		420		425		430									
Leu	Glu	Gln	Ser	Lys	Arg	Ala	Lys	Tyr	Phe	Ile	Asn	Ser	Lys	Gly	Ile
	435			440		445									
Pro	Arg	Tyr	Cys	Ser	Val	Thr	Thr	Gln	Ala	Asp	Gly	Arg	Val	Val	Leu
	450			455		460									
Val	Gly	Gly	Arg	Ser	Arg	Arg	Gly	Lys	Lys	Arg	Gly	Pro	Pro	Gly	Ser
465		470		475		480									
Lys	Asp	Trp	Gly	Thr	Ala	Leu	Lys	Gly	Cys	Asp	Asp	Tyr	Leu	Phe	Ile
		485		490		495									

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Glu Phe Leu Lys Arg Cys Leu His Trp Asp Pro Ser Ala Arg Leu Thr
 500 505 510
 Pro Ala Gln Ala Leu Arg His Pro Trp Ile Ser Lys Ser Val Pro Arg
 515 520 525
 Pro Leu Thr Thr Ile Asp Lys Val Ser Gly Lys Arg Val Val Asn Pro
 530 535 540
 Ala Ser Ala Phe Gln Gly Leu Gly Ser Lys Leu Pro Pro Val Val Gly
 545 550 555 560
 Ile Ala Asn Lys Leu Lys Ala Asn Leu Met Ser Glu Thr Asn Gly Ser
 565 570 575
 Ile Pro Leu Cys Ser Val Leu Pro Lys Leu Ile Ser
 580 585

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2327 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Other

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CGGCGCTGGC	AAGCGAAGCT	TGGGGGTGGG	GAGGTAGAGT	GAGCCCTCAG	TAGGAGGGAC	60
GAGGGCAGGG	GTCTGACTGC	CTCCCCGGGA	CCGCCCCCAC	CTCCTCTCTA	TCAGGGCCCC	120
CTCCCCCAT	CCCTGTCTCA	CCGGGCGCGG	GGGACGGGGC	TAGAGCGGAG	TTAGAGCAAG	180
AAGAATTTCC	ACCCCTGGAT	TCCCTCTGAA	ACCCTAGATC	GGGGTATATG	TTAAGGGATT	240
ACGAAAATCT	AGGACTTTTT	GTGGGGCTTT	TTATTAAAGG	GGGGGAGCCC	GGGAGCAATA	300
CCTTGGAAG	AAGCCCTGTT	GCTTAGAGCG	GATAACCAAC	GGCTGAACTC	TTGGGGTTTG	360
CTGTGAGGGG	TGCGGTCTAG	CTTCGAATGT	ACAGTGGTGG	AGCCACAGTG	TTAAAGAACA	420
GAGAAGTGAT	CCTTAATCAT	TTAGAATTTT	GCCTCCACCA	TCCACCAGAA	AATGAAGTGG	480
AAAGAGAAGT	TGGGGGATGG	TGTCTATGAC	ACCTTCATGA	TGATAGATGA	AACCAAATGT	540
CCCCCCTGTT	CAAATGTACT	CTGCAATCCT	TCTGAACCAC	CTCCACCCAG	AAGACTAAAT	600
ATGACCACTG	AGCAGTTTAC	AGGAGATCAT	ACTCAGCACT	TTTTGGATGG	AGGTGAGATG	660
AAGGTAGAAC	AGCTGTTTCA	AGAATTTGGC	AACAGAAAAT	CCAATACTAT	TCAGTCAGAT	720
GGCATCAGTG	ACTCTGAAAA	ATGCTCTCCT	ACTGTTTCTC	AGGGTAAAAG	TTCAGATTGC	780
TTGAATACAG	TAAAATCCAA	CAGTTCATCC	AAGGCACCCA	AAGTGGTGCC	TCTGACTCCA	840
GAACAAGCCC	TGAAGCAATA	TAAACACCAC	CTCACTGCCT	ATGAGAAACT	GGAAATAATT	900
AATTATCCAG	AAATTTACTT	TGTAGGTCCA	AATGCCAAGA	AAAGACATGG	AGTTATTGGT	960
GGTCCCAATA	ATGGAGGGTA	TGATGATGCA	GATGGGGCCT	ATATTCATGT	ACCTCGAGAC	1020
CATCTAGCTT	ATCGATATGA	GGTGCTGAAA	ATTATTGGCA	AGGGGAGTTT	TGGGCAGGTG	1080

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GCCAGGGTCT ATGATCACAA ACTTCGACAG TACGTGGCCC TAAAAATGGT GCGCAATGAG 1140
AAGCGCTTTC ATCGTCAAGC AGCTGAGGAG ATCCGGATTT TGGAGCATCT TAAGAAACAG 1200
GATAAAACTG GTAGTATGAA CGTTATCCAC ATGCTGGAAA GTTTCACATT CCGGAACCAT 1260
GTTTGCATGG CCTTTGAATT GCTGAGCATA GACCTTTATG AGCTGATTAA AAAAAATAAG 1320
TTTCAGGGTT TTAGCGTCCA GTTGGTACGC AAGTTTGCCC AGTCCATCTT GCAATCTTTG 1380
GATGCCCTCC ACAAAAATAA GATTATTAC TGCATCTGA AGCCAGAAAA CATTCTCCTG 1440
AAACACCACG GGCGCAGTTC AACCAAGGTC ATTGACTTTG GGTCCAGCTG TTTCGAGTAC 1500
CAGAAGCTCT ACACATATAT CCAGTCTCGG TTCTACAGAG CTCCAGAAAT CATCTTAGGA 1560
AGCCGCTACA GCACACCAAT TGACATATGG AGTTTTGGCT GCATCCTTGC AGAACTTTTA 1620
ACAGGACAGC CTCTCTTCCC TGGAGAGGAT GAAGGAGACC AGTTGGCCTC CATGATGGAG 1680
CTTCTAGGGA TGCCACCACC AAAACTTCTG GAGCAATCCA AACGTGCCAA GTACTTTATT 1740
AATTCCAAGG GCATACCCCG CTACTGCTCT GTGACTACCC AGGCAGATGG GAGGGTTGTG 1800
CTTGTGGGGG GTCGCTCACG TAGGGGTAAA AAGCGGGGTC CCCCAGGCAG CAAAGACTGG 1860
GGGACAGCAC TGAAAGGGTG TGATGACTAC TTGTTTATAG AGTTCTTGAA AAGGTGTCTT 1920
CACTGGGACC CCTCTGCCCC CTTGACCCCA GCTCAAGCAT TAAGACACCC TTGGATTAGC 1980
AAGTCTGTCC CCAGACCTCT CACCACCATA GACAAGGTGT CAGGGAAACG GGTAGTTAAT 2040
CCTGCAAGTG CTTTCCAGGG ATTGGGTTCT AAGCTGCCTC CAGTTGTTGG AATAGCCAAT 2100
AAGCTTAAAG CTAACCTAAT GTCAGAAACC AATGGTAGTA TACCCTATG CAGTGTATTG 2160
CCAAACTGA TTAGCTAGTG GACAGAGATA TGCCCAGAGA TGCATATGTG TATATTTTTA 2220
TGATCTTACA AACCTGCAAA TGGAAAAAAT GCAAGCCCAT TGGTGGATGT TTTTGTTAGA 2280
GTAGACTTTT TTAAACAAG ACAAACATT TTTATATGAT TATAAAA 2327

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(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 568 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```

Met Lys Trp Lys Glu Lys Leu Gly Asp Gly Val Tyr Asp Thr Phe Met
 1             5             10             15
Met Ile Asp Glu Thr Lys Cys Pro Pro Cys Ser Asn Val Leu Cys Asn
          20             25             30
Pro Ser Glu Pro Pro Pro Pro Arg Arg Leu Asn Met Thr Thr Glu Gln
          35             40             45
Phe Thr Gly Asp His Thr Gln His Phe Leu Asp Gly Gly Glu Met Lys
          50             55             60
Val Glu Gln Leu Phe Gln Glu Phe Gly Asn Arg Lys Ser Asn Thr Ile

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65					70						75					80
Gln	Ser	Asp	Gly	Ile	Ser	Asp	Ser	Glu	Lys	Cys	Ser	Pro	Thr	Val	Ser	
				85					90					95		
Gln	Gly	Lys	Ser	Ser	Asp	Cys	Leu	Asn	Thr	Val	Lys	Ser	Asn	Ser	Ser	
			100					105					110			
Ser	Lys	Ala	Pro	Lys	Val	Val	Pro	Leu	Thr	Pro	Glu	Gln	Ala	Leu	Lys	
		115					120					125				
Gln	Tyr	Lys	His	His	Leu	Thr	Ala	Tyr	Glu	Lys	Leu	Glu	Ile	Ile	Asn	
	130					135					140					
Tyr	Pro	Glu	Ile	Tyr	Phe	Val	Gly	Pro	Asn	Ala	Lys	Lys	Arg	His	Gly	
145					150				155					160		
Val	Ile	Gly	Gly	Pro	Asn	Asn	Gly	Gly	Tyr	Asp	Asp	Ala	Asp	Gly	Ala	
			165					170					175			
Tyr	Ile	His	Val	Pro	Arg	Asp	His	Leu	Ala	Tyr	Arg	Tyr	Glu	Val	Leu	
		180					185					190				
Lys	Ile	Ile	Gly	Lys	Gly	Ser	Phe	Gly	Gln	Val	Ala	Arg	Val	Tyr	Asp	
	195					200					205					
His	Lys	Leu	Arg	Gln	Tyr	Val	Ala	Leu	Lys	Met	Val	Arg	Asn	Glu	Lys	
	210				215						220					
Arg	Phe	His	Arg	Gln	Ala	Ala	Glu	Glu	Ile	Arg	Ile	Leu	Glu	His	Leu	
225				230					235					240		
Lys	Lys	Gln	Asp	Lys	Thr	Gly	Ser	Met	Asn	Val	Ile	His	Met	Leu	Glu	
			245					250				255				
Ser	Phe	Thr	Phe	Arg	Asn	His	Val	Cys	Met	Ala	Phe	Glu	Leu	Leu	Ser	
		260					265					270				
Ile	Asp	Leu	Tyr	Glu	Leu	Ile	Lys	Lys	Asn	Lys	Phe	Gln	Gly	Phe	Ser	
	275					280						285				
Val	Gln	Leu	Val	Arg	Lys	Phe	Ala	Gln	Ser	Ile	Leu	Gln	Ser	Leu	Asp	
	290				295						300					
Ala	Leu	His	Lys	Asn	Lys	Ile	Ile	His	Cys	Asp	Leu	Lys	Pro	Glu	Asn	
305				310					315					320		
Ile	Leu	Leu	Lys	His	His	Gly	Arg	Ser	Ser	Thr	Lys	Val	Ile	Asp	Phe	
			325					330				335				
Gly	Ser	Ser	Cys	Phe	Glu	Tyr	Gln	Lys	Leu	Tyr	Thr	Tyr	Ile	Gln	Ser	
		340					345					350				
Arg	Phe	Tyr	Arg	Ala	Pro	Glu	Ile	Ile	Leu	Gly	Ser	Arg	Tyr	Ser	Thr	
	355					360					365					
Pro	Ile	Asp	Ile	Trp	Ser	Phe	Gly	Cys	Ile	Leu	Ala	Glu	Leu	Leu	Thr	
	370				375						380					
Gly	Gln	Pro	Leu	Phe	Pro	Gly	Glu	Asp	Glu	Gly	Asp	Gln	Leu	Ala	Ser	
385				390					395					400		
Met	Met	Glu	Leu	Leu	Gly	Met	Pro	Pro	Pro	Lys	Leu	Leu	Glu	Gln	Ser	
			405					410					415			

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Lys	Arg	Ala	Lys	Tyr	Phe	Ile	Asn	Ser	Lys	Gly	Ile	Pro	Arg	Tyr	Cys	
			420					425					430			
Ser	Val	Thr	Thr	Gln	Ala	Asp	Gly	Arg	Val	Val	Leu	Val	Gly	Gly	Arg	
		435					440					445				
Ser	Arg	Arg	Gly	Lys	Lys	Arg	Gly	Pro	Pro	Gly	Ser	Lys	Asp	Trp	Gly	
		450				455					460					
Thr	Ala	Leu	Lys	Gly	Cys	Asp	Asp	Tyr	Leu	Phe	Ile	Glu	Phe	Leu	Lys	
465					470					475					480	
Arg	Cys	Leu	His	Trp	Asp	Pro	Ser	Ala	Arg	Leu	Thr	Pro	Ala	Gln	Ala	
			485					490						495		
Leu	Arg	His	Pro	Trp	Ile	Ser	Lys	Ser	Val	Pro	Arg	Pro	Leu	Thr	Thr	
		500					505						510			
Ile	Asp	Lys	Val	Ser	Gly	Lys	Arg	Val	Val	Asn	Pro	Ala	Ser	Ala	Phe	
		515					520					525				
Gln	Gly	Leu	Gly	Ser	Lys	Leu	Pro	Pro	Val	Val	Gly	Ile	Ala	Asn	Lys	
		530				535					540					
Leu	Lys	Ala	Asn	Leu	Met	Ser	Glu	Thr	Asn	Gly	Ser	Ile	Pro	Leu	Cys	
545				550						555					560	
Ser	Val	Leu	Pro	Lys	Leu	Ile	Ser									
				565												

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What is claimed is:

1. An isolated polynucleotide comprising a nucleotide sequence encoding the polypeptide of SEQ ID NO: 2 or 4; or a nucleotide sequence complementary to said nucleotide sequence.
2. The polynucleotide of claim 1 which is DNA or RNA.
3. The polynucleotide of claim 1 wherein said nucleotide sequence comprises the polypeptide encoding sequence contained in SEQ ID NO: 1 or 3.
4. An isolated polynucleotide comprising the nucleotide sequence of SEQ ID NO: 1 or 3.
5. An expression system comprising a DNA or RNA molecule, wherein said expression system is capable of producing the polypeptide comprising the amino acid of SEQ ID NO: 2 or 4, when said expression system is present in a compatible host cell.
6. A host cell comprising the expression system of claim 5.
7. A process for producing a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or 4 comprising culturing the host cell of claim 6 and under conditions sufficient for the production of said polypeptide.
8. The process of claim 7 which further includes recovering the polypeptide from the culture.
9. A process for producing a cell which produces a polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or 4 comprising transforming or transfecting a host cell with the expression system of claim 5 such that the host cell, under appropriate culture conditions, produces the polypeptide.

10. Cells produced by the process of claim 9.
11. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:2 or 4.
12. A polypeptide prepared by the method of claim 8.
13. An antibody immunospecific for the polypeptide of claim 11.
14. A polypeptide obtainable by expressing a nucleotide sequence comprising that of SEQ ID NO: 1 or 3.

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FIGURE 1. Nucleotide and Amino Acid sequence from a hYAK3 α (SEQ ID NOS: 1 and 2, respectively.)

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1  GGAGCGAAATGCGCTGAGCTGCAGTGTCTGGTCGAGAGTACCCGTGGGAGCGTCGCGCCG      60
61  CGGAGGCAGCCGTCCCGGGCGTAGGTGGCGTGGCCGACCCGACCCCCAACTGGCGCCTCTC      120
121  CCCGCGCGGGGTCCCGAGCTAGGAGATGGGAGGCACAGCTCGTGGGCCTGGGCGGAAGGA      180
      M G G T A R G P G R K D
181  TCGGGGGCCGCCTGGGGCCGGGCTCCCGCCCCAGCAGCGGAGGTTGGGGGATGGTGTCTA      240
      A G P P G A G L P P Q Q R R L G D G V
241  TGACACCTTCATGATGATAGATGAAACCAAATGTCCCCCTGTTCAAATGTACTCTGCAA      300
      D T F M M I D E T K C P P C S N V L C N
301  TCCTTCTGAACCACCTCCACCCAGAAGACTAAATATGACCACTGAGCAGTTTACAGGAGA      360
      P S E P P P P R R L N M T T E Q F T G D
361  TCATACTCAGCACTTTTTTGGATGGAGGTGAGATGAAGGTAGAACAGCTGTTTCAAGAATT      420
      H T Q H F L D G G E M K V E Q L F Q E F
421  TGGCAACAGAAAATCCAATACTATTTCAGTCAGATGGCATCAGTGACTCTGAAAAATGCTC      480
      G N R K S N T I Q S D G I S D S E K C S
481  TCCTACTGTTTCTCAGGGTAAAAGTTCAGATTGCTTGAATACAGTAAAATCCAACAGTTC      540
      P T V S Q G K S S D C L N T V K S N S S
541  ATCCAAGGCACCCAAAGTGGTGCCTCTGACTCCAGAACAAGCCCTGAAGCAATATAAACA      600
      S K A P K V V P L T P E Q A L K Q Y K H
601  CCACCTCACTGCCTATGAGAACTGGAAATAATTAATTATCCAGAAATTTACTTTGTAGG      660
      H L T A Y E K L E I I N Y P E I Y F V G
661  TCCAAATGCCAAGAAAAGACATGGAGTTATTGGTGGTCCCAATAATGGAGGGTATGATGA      720
      P N A K K R H G V I G G P N N G G Y D D
721  TGCAGATGGGGCCTATATTCATGTACCTCGAGACCATCTAGCTTATCGATATGAGGTGCT      780
      A D G A Y I H V P R D H L A Y R Y E V L
781  GAAAATTATTGGCAAGGGGAGTTTTGGGCAGGTGGCCAGGGTCTATGATCACAACTTCG      840
      K I I G K G S F G Q V A R V Y D H K L R
841  ACAGTACGTGGCCCTAAAAATGGTGCACAATGAGAAGCGCTTTCATCGTCAAGCAGCTGA      900
      Q Y V A L K M V R N E K R F H R Q A A E
901  GGAGATCCGGATTTTGGAGCATCTTAAGAAACAGGATAAACTGGTAGTATGAACGTTAT      960
      E I R I L E H L K K Q D K T G S M N V I
961  CCACATGCTGGAAAGTTTTCACATTCGGAACCATGTTTGCATGGCCTTTGAATTGCTGAG      1020
      H M L E S F T F R N H V C M A F E L L S
1021  CATAGACCTTTATGAGCTGATTAATAAAAAATAAGTTTCAGGGTTTTAGCGTCCAGTTGGT      1080
      I D L Y E L I K K N K F Q G F S V Q L V
1081  ACGCAAGTTTGCCCAGTCCATCTTGCAATCTTTGGATGCCCTCCACAAAAATAAGATTAT      1140
      R K F A Q S I L Q S L D A L H K N K I I
1141  TCACTGCGATCTGAAGCCAGAAAACATTCTCCTGAAACACCACGGGCGCAGTTCAACCAA      1200
      H C D L K P E N I L L K H H G R S S T K
1201  GGTCAATTGACTTTGGGTCCAGCTGTTTCGAGTACCAGAAGCTCTACACATATATCCAGTC      1260
      V I D F G S S C F E Y Q K L Y T Y I Q S
1261  TCGGTTCTACAGAGCTCCAGAAATCATCTTAGGAAGCCGCTACAGCACACCAATTGACAT      1320
      R F Y R A P E I I L G S R Y S T P I D I
1321  ATGGAGTTTTGGCTGCATCCTTGCAGAACTTTTAACAGGACAGCCTCTCTCCCTGGAGA      1380
      W S F G C I L A E L L T G Q P L F P G E
1381  GGATGAAGGAGACCAGTTGGCCTCCATGATGGAGCTTCTAGGGATGCCACCACCAAACT      1440
      D E G D Q L A S M M E L L G M P P P K L
1441  TCTGGAGCAATCCAAACGTGCCAAGTACTTTATTAATTCCAAGGCATACCCCGCTACTG      1500

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FIGURE 2. Nucleotide and Amino Acid sequence from a hYAK3b (SEQ ID NOS: 3 and 4, respectively.)

1	CGGCGCTGGCAAGCGAAGCTTGGGGGTGGGGAGGTAGAGTGAGCCCTCAGTAGGAGGGAC	60
61	GAGGGCAGGGGTCTGACTGCCTCCCCGGGACCGCCCCACCTCCTCTCTATCAGGGCCCC	120
121	CTCCCCCATCCCTGTCTCACCGGGCGCGGGGGACGGGGCTAGAGCGGAGTTAGAGCAAG	180
181	AAGAATTTCCACCCCTGGATTCCCTCTGAAACCCCTAGATCGGGGTATATGTTAAGGGATT	240
241	ACGAAAATCTAGGACTTTTTGTGGGGCTTTTTATTAAAGGGGGGGAGCCCGGGAGCAATA	300
301	CCTTGGAAGAAGCCCTGTTGCTTAGAGCGGATAACCAACGGCTGAACTCTTGGGGTTTG	360
361	CTGTGAGGGGTGCGGTCTAGCTTCGAATGTACAGTGGTGGAGCCACAGTGTTAAAGAACA	420
421	GAGAAGTGATCCTTAATCATTTAGAAATTTGCCTCCACCATCCACCAGAAAATGAAGTGG	480
	M K W	
481	AAAGAGAAGTTGGGGGATGGTGTCTATGACACCTTCATGATGATAGATGAAACCAAATGT	540
	K E K L G D G V Y D T F M M I D E T K C	
541	CCCCCTGTTCAAATGTACTCTGCAATCCTTCTGAACCACCTCCACCCAGAAGACTAAAT	600
	P P C S N V L C N P S E P P P P R R L N	
601	ATGACCACTGAGCAGTTTACAGGAGATCATACTCAGCACTTTTTTGGATGGAGGTGAGATG	660
	M T T E Q F T G D H T Q H F L D G G E M	
661	AAGGTAGAACAGCTGTTTCAAGAATTTGGCAACAGAAAATCCAATACTATTTCAGTCAGAT	720
	K V E Q L F Q E F G N R K S N T I Q S D	
721	GGCATCAGTGACTCTGAAAAATGCTCTCCTACTGTTTCTCAGGGTAAAAGTTCAGATTGC	780
	G I S D S E K C S P T V S Q G K S S D C	
781	TTGAATACAGTAAAATCCAACAGTTCATCCAAGGCACCCAAAGTGGTGCCTCTGACTCCA	840
	L N T V K S N S S S K A P K V V P L T P	
841	GAACAAGCCCTGAAGCAATATAAACACCACCTCACTGCCTATGAGAACTGGAAATAATT	900
	E Q A L K Q Y K H H L T A Y E K L E I I	
901	AATTATCCAGAAATTTACTTTGTAGGTCCAAATGCCAAGAAAAGACATGGAGTTATTGGT	960
	N Y P E I Y F V G P N A K K R H G V I G	
961	GGTCCCAATAATGGAGGGTATGATGATGCAGATGGGGCCTATATTCATGTACCTCGAGAC	1020
	G P N N G G Y D D A D G A Y I H V P R D	
1021	CATCTAGCTTATCGATATGAGGTGCTGAAAATTATTGGCAAGGGGAGTTTTGGGCAGGTG	1080
	H L A Y R Y E V L K I I G K G S F G Q V	
1081	GCCAGGGTCTATGATCACAACCTTCGACAGTACGTGGCCCTAAAAATGGTGCAGCAATGAG	1140
	A R V Y D H K L R Q Y V A L K M V R N E	
1141	AAGCGCTTTCATCGTCAAGCAGCTGAGGAGATCCGGATTTTGGAGCATCTTAAGAAACAG	1200
	K R F H R Q A A E E I R I L E H L K K Q	
1201	GATAAACTGGTAGTATGAACGTTATCCACATGCTGGAAAGTTTCACATTCCGGAACCAT	1260
	D K T G S M N V I H M L E S F T F R N H	
1261	GTTTGCATGGCCTTTGAATTGCTGAGCATAGACCTTTATGAGCTGATTAAAAAAATAAG	1320
	V C M A F E L L S I D L Y E L I K K N K	
1321	TTTCAGGGTTTTAGCGTCCAGTTGGTACGCAAGTTTGCCCAGTCCATCTTGCAATCTTTG	1380
	F Q G F S V Q L V R K F A Q S I L Q S L	
1381	GATGCCCTCCACAAAAATAAGATTATTCAGTGCATCTGAAGCCAGAAAACATTCTCCTG	1440
	D A L H K N K I I H C D L K P E N I L L	
1441	AAACACCACGGGCGCAGTTCAACCAAGGTCATTGACTTTGGGTCCAGCTGTTTCGAGTAC	1500
	K H H G R S S T K V I D F G S S C F E Y	
1501	CAGAAGCTCTACACATATATCCAGTCTCGGTTCTACAGAGCTCCAGAAATCATCTTAGGA	1560

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Q K L Y T Y I Q S R F Y R A P E I I L G
 1561 AGCCGCTACAGCACACCAATTGACATATGGAGTTTTGGCTGCATCCTTGCAGAACTTTTA 1620
 S R Y S T P I D I W S F G C I L A E L L
 1621 ACAGGACAGCCTCTCTTCCCTGGAGAGGATGAAGGAGACCAGTTGGCCTCCATGATGGAG 1680
 T G Q P L F P G E D E G D Q L A S M M E
 1681 CTTCTAGGGATGCCACCACCAAACTTCTGGAGCAATCCAAACGTGCCAAGTACTTTATT 1740
 L L G M P P P K L L E Q S K R A K Y F I
 1741 AATCCAAGGGCATAACCCGCTACTGCTCTGTGACTACCCAGGCAGATGGGAGGGTTGTG 1800
 N S K G I P R Y C S V T T Q A D G R V V
 1801 CTTGTGGGGGGTCGCTCACGTAGGGGTAAAAAGCGGGGTCCCCCAGGCAGCAAAGACTGG 1860
 L V G G R S R R G K K R G P P G S K D W
 1861 GGGACAGCACTGAAAGGGTGTGATGACTACTTGTGTTTATAGAGTTCTTGAAAAGGTGTCTT 1920
 G T A L K G C D D Y L F I E F L K R C L
 1921 CACTGGGACCCCTCTGCCCCGCTTGACCCAGCTCAAGCATTAAGACACCCCTTGGATTAGC 1980
 H W D P S A R L T P A Q A L R H P W I S
 1981 AAGTCTGTCCCCAGACCTCTCACCACCATAGACAAGGTGTCAGGGAAACGGGTAGTTAAT 2040
 K S V P R P L T T I D K V S G K R V V N
 2041 CCTGCAAGTGCTTTCCAGGGATTGGGTTCTAAGCTGCCTCCAGTTGTTGGAATAGCCAAT 2100
 P A S A F Q G L G S K L P P V V G I A N
 2101 AAGCTTAAAGCTAACTTAATGTCAGAAACCAATGGTAGTATACCCCTATGCAGTGTATTG 2160
 K L K A N L M S E T N G S I P L C S V L
 2161 CCAAACTGATTAGCTAGTGGACAGAGATATGCCAGAGATGCATATGTGTATATTTTTA 2220
 P K L I S
 2221 TGATCTTACAAACCTGCAAATGGAAAAAATGCAAGCCCATTGGTGGATGTTTTTGTTAGA 2280
 2281 GTAGACTTTTTTTTAAACAAGACAAAACATTTTTATATGATTATAAAA 2327

Nucleotide and Amino Acid sequence from a hYAK3α (SEQ ID NOS: 1 and 2, respectively.)

1	GGAGCGAAATGCGCTGAGCTGCAGTGTCTGCTCGAGAGTACCCGTTGGGAGCGTCCGCGCCG	60
61	CGGAGGCAGCCGTTCCCGGCGTAGGTGGCGTGGCCGACCCGACCCCACTGGCGCCTCTC	120
121	CCCGCGCGGGGTCCCGAGCTAGGAGATGGGAGGCACAGCTCGTGGGCCTGGCGCGAAGGA	180
	M G G T A R G P G R K D	
181	TGCGGGGCGCGCTGGGGCCGGGCTCCCGCCCCAGCAGCGAGGTTGGGGGATGGTGTCTA	240
	A G P P G A G L P P Q Q R R L G D G V	
241	TGACACCTTCATGATGATAGATGAAACCAAATGTCCCCCCTGTTCAAATGTACTCTGCAA	300
	D T F M M I D E T K C P P C S N V L C N	
301	TCCTTCTGAACCACCTCCACCCAGAAGACTAAATATGACCACTGAGCAGTTTACAGGAGA	360
	P S E P P P P R R L N M T T E Q F T G D	
361	TCATACTCAGCACTTTTTGGATGGAGGTGAGATGAAGGTAGAACAGCTGTTTCAAGAATT	420
	H T Q H F L D G G E M K V E Q L F Q E F	
421	TGGCAACAGAAATCCAATACTATTTCAGTCAGATGGCATCAGTCACTCTGAAAATGCTC	480
	G N R K S N T I Q S D G I S D S E K C S	
481	TCCTACTGTTTCTCAGGGTAAAAGTTCAGATTGCTTGAATACAGTAAAATCCAACAGTTC	540
	P T V S Q G K S S D C L N T V K S N S S	
541	ATCCAAGGCACCCAAAGTGGTGCCTCTGACTCCAGAACCAAGCCCTGAAGCAATATAACA	600
	S K A P K V V P L T P E Q A L K Q Y K H	
601	CCACCTCACTGCCTATGAGAACTGGAATAATTAATTATCCAGAAATTTACTTTGTAGG	660
	H L T A Y E K L E I I N Y P E I Y F V G	
661	TCCAAATGCCAAGAAAAGACATGGAGTTATTGGTGGTCCCAATAATGGAGGGTATGATGA	720
	P N A K K R H G V I Q G P N N G G Y D D	
721	TGCAGATGGGGCCTATATTCATGTACCTCGAGACCATCTAGCTTATCGATATGAGGTGCT	780
	A D G A Y I H V P R D H L A Y R Y E V L	
781	GAAAATTATTGGCAAGGGGAGTTTTGGGCAGGTGGCCAGGGTCTATGATCACAACTTCG	840
	K I I G K G S F G Q V A R V Y D H K L R	
841	ACAGTACGTGGCCCTAAAAATGGTGGCAATGAGAAGCGCTTTCATCGTCAAGCAGCTGA	900
	Q Y V A L K M V R N E K R F H R Q A A E	
901	GGAGATCCGGATTTTGGAGCATCTTAAGAAACAGGATAAAACTGGTAGTATGAACGTTAT	960
	E I R I L E H L K K Q D K T G S M N V I	
961	CCACATGCTGGAAAGTTTCACATTCCCGGAACCATGTTTGCATGGCCTTTGAATTGCTGAG	1020
	H M L E S F T F R N H V C M A F E L L S	
1021	CATAGACCTTTATGAGCTGATTAAAAAAATAAGTTTCAGGGTTTTAGCGTCCAGTTGGT	1080
	I D L Y E L I K K N K F Q G F S V Q L V	
1081	ACGCAAGTTTGGCCAGTCCATCTTGCAATCTTTGGATGCCCTCCACAAAAATAAGATTAT	1140
	R K F A Q S I L Q S L D A L H K N K I I	
1141	TCACTGCGATCTGAAGCCAGAAAACATTCTCCTGAAACACCACGGGCGCAGTTCAACCAA	1200
	H C D L K P E N I L L K H H G R S S T K	
1201	GGTCATTGACTTTGGGTCCAGCTGTTTCGAGTACCAGAAGCTCTACACATATATCCAGTC	1260
	V I D F G S S C F E Y Q K L Y T Y I Q S	
1261	TCGGTTCTACAGAGCTCCAGAAATCATCTTAGGAAGCCGCTACAGCACACCAATTGACAT	1320
	R F Y R A P E I I L G S R Y S T F I D I	
1321	ATGGAGTTTTGGCTGCATCCTTGCAGAACTTTTAACAGGACAGCCTCTCTCCCTGGAGA	1380
	W S F G C I L A E L L T G Q P L F P G E	
1381	GGATGAAGGAGACCAGTTGGCCTCCATGATGGAGCTTCTAGGGATGCCACCACCAAACT	1440
	D E G D Q L A S M M E L L G M P P P K L	
1441	TCTGGAGCAATCCAAACGTGCCAAGTACTTTATTAAATCCAAAGGCATACCCCGCTACTG	1500
	L E Q S K R A K Y F I N S K G I P R Y C	
1501	CTCTGTGACTACCCAGGCAGATGGGAGGGTTGTGCTTGTGGGGGTCGCTCACGTAGGGG	1560
	S V T T Q A D G R V V L V G G R S R R G	
1561	TAAAAAGCGGGGTCCCCCAGGCAGCAAAGACTGGGGGACAGCACTGAAAGGGTGTGATGA	1620
	K K R G P P G S K D W G T A L K G C D D	
1621	CTACTTGTTTATAGAGTTCTTGAAAAGGTGTCTTCACTGGGACCCCTCTGCCCGCTTGAC	1680
	Y L F I E F L K R C L H W D P S A R L T	
1681	CCCAGCTCAAGCATTAAGACACCCTTGGATTAGCAAGTCTGTCCCCAGACCTCTCACCAC	1740
	P A Q A L R H P W I S K S V P R P L T T	
1741	CATAGACAAGGTGTCAGGGAAACGGGTAGTTAATCCTGCAAGTGCTTTCCAGGGATTGGG	1800
	I D K V S G K R V V N P A S A F Q G L G	
1801	TTCTAAGCTGCCTCCAGTTGTTGGAATAGCCAATAAGCTTAAAGCTAACTTAATGTCAGA	1860
	S K L P F V V G I A N K L K A N L M S E	
1861	AACCAATGGTAGTATACCCCTATGCAGTGTATTGCCAAAAGTGAATTAGCTAGTGGACAGA	1920
	T N G S I P L C S V L P K L I S	
1921	GATATGCCCAGAGATGCATATGTGTATATTTTATGATCTTACAAACCTGCAATGGAAA	1980
1981	AAATGCAAGCCCATTTGGTGGATGTTTTTGTAGAGTAGACTTTTTTTTAAACAAGACAAA	2040
2041	CATTTTTATATGATTATAAAA	2061