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(30) 1997/09/25 (08/937,466) US

(54) **GENES UCP3**
(54) **UCP3 GENES**

(57) L'invention concerne des méthodes et des compositions relatives à une nouvelle famille de gènes, les mUCP3, impliqués dans la régulation métabolique. Les polypeptides peuvent être produits de manière recombinée à partir de cellules hôtes transformées tirées d'acides nucléiques codant les mUCP3 décrits ou purifiés à partir de cellules mammifères. L'invention concerne des sondes isolées d'hybridation de mUCP3, des constructions inactivées/activées et des amorces capables de s'hybrider spécifiquement aux gènes mUPC3 décrits, et des agents de liaison spécifiques au mUCP3 tels que des anticorps spécifiques, des animaux et des cellules modifiées par les acides nucléiques de mUCP3 de l'invention, et des méthodes de production et d'utilisation des compositions de l'invention dans l'industrie biopharmaceutique.

(57) The invention provides methods and compositions relating to a novel family of genes, mUCP3s, involved in metabolic regulation. The polypeptides may be produced recombinantly from transformed host cells from the disclosed mUCP3 encoding nucleic acids or purified from mammalian cells. The invention provides isolated mUCP3 hybridization probes, knock-out/in constructs and primers capable of specifically hybridizing with the disclosed mUCP3 genes, mUCP3-specific binding agents such as specific antibodies, animals and cells modified with the subject mUCP3 nucleic acids, and methods of making and using the subject compositions in the biopharmaceutical industry.

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(54) **Title:** UCP3 GENES

(57) **Abstract**

The invention provides methods and compositions relating to a novel family of genes, mUCP3s, involved in metabolic regulation. The polypeptides may be produced recombinantly from transformed host cells from the disclosed mUCP3 encoding nucleic acids or purified from mammalian cells. The invention provides isolated mUCP3 hybridization probes, knock–out/in constructs and primers capable of specifically hybridizing with the disclosed mUCP3 genes, mUCP3–specific binding agents such as specific antibodies, animals and cells modified with the subject mUCP3 nucleic acids, and methods of making and using the subject compositions in the biopharmaceutical industry.

UCP3 Genes

INTRODUCTION

Field of the Invention

The field of this invention is UCP3 genes and their use in biotechnology.

Background

A mitochondrial protein called uncoupling protein (UCP1) is thought to play an important role in the body's regulation of energy utilization. Such regulation provides wide spread physiological controls including body weight, appetite, glucose metabolism, temperature, immune responses, etc.. Mechanistically, UCP1 is thought to create a pathway that allows dissipation of the proton electrochemical gradient across the inner mitochondrial membrane in brown adipose tissue, without coupling to any other energy consuming process (for review, see Nicholis & Locke (1984) Physiol Rev 64, 1-64). Unfortunately, the role of UCP1 in physiologies such as body weight regulation in large adult mammals such as people, cattle, pigs, etc. is likely to be limited, since there is little brown adipose tissue in such animals.

UCP2 is a second, related uncoupling protein that is much more widely expressed in large adult mammals (see, e.g. Fleury et al. (1997) Nature Genetics 15, 269-272 and Tartaglia et al. (1996) WO96/05861). Consistent with a role in the regulation of energy utilization generally, and in diabetes and obesity in particular, the UCP2 gene is upregulated in response to fat feeding and maps to regions of the human and mouse genomes linked to hyperinsulinaemia and obesity. More recently, a third structurally related UCP gene, hUCP3 has been charaterized and found to be preferentially expressed in skeletal muscle and brown adipose tissues; see, Vidal-Puig et al. (1997) BBRC 235, 79-82 and Boss et al. (1997) FEBS Letters 408, 39-42.

SUMMARY OF THE INVENTION

The invention provides methods and compositions relating to isolated mUCP3 polypeptides, related nucleic acids, polypeptide domains thereof having mUCP3-specific structure and activity and modulators of mUCP3 function. mUCP3 polypeptides and

modulators of mUCP3 expresssion and/or function can regulate mitochodrial respiration and hence provide important regulators of cell metabolism and function. The polypeptides may be produced recombinantly from transformed host cells from the subject mUCP3 polypeptide encoding nucleic acids or purified from mammalian cells. The invention provides isolated mUCP3 hybridization probes and primers capable of specifically hybridizing with the disclosed mUCP3 genes, mUCP3-specific binding agents such as specific antibodies, and methods of making and using the subject compositions in diagnosis (e.g. genetic hybridization screens for mUCP3 transcripts) and in the biopharmaceutical industry (e.g. as immunogens, reagents for isolating other transcriptional regulators, knockin/out vectors, transgenic animals anc cell lines, reagents for screening chemical libraries for lead pharmacological agents, etc.).

BRIEF DESCRIPTION OF THE FIGURES

Fig. 1 shows the amino acid sequence of a mUCP3a polypeptide (SEQ ID NO:2), indicating mUCP3a-specific sequences and domains in common with hUCP3.

Fig. 2 shows the nucleotide sequence of a mUCP3a-encoding cDNA (SEQ ID NO:1), indicating mUCP3a-specific sequences and domains in common with hUCP3.

Fig. 3 shows the structures of mUCP3 isoforms a, b and c.

DETAILED DESCRIPTION OF THE INVENTION

Exemplary nucleotide sequences of natural cDNAs encoding mUCP3 polypeptides are shown as SEQ ID NO:1, 3 and 5, and their full conceptual translates are shown as SEQ ID NOS:2, 4 and 6, respectively. The mUCP3 polypeptides of the invention include incomplete translates of SEQ ID NOS:1, 3 and 5 which translates and deletion mutants of SEQ ID NOS:2, 4 and 6 have mUCP3-specific amino acid sequence, binding specificity or function. Preferred translates/deletion mutants comprise at least a 6, preferably at least an 8, more preferably at least a 10, most preferably at least a 12 residue domain of the translates not found in hUCP3. Such domains are readily discernable from alignments of mUCP3 polypeptides and hUCP3. See, e.g. Fig 1 for the mUCP3a amino acid domains in common (bold) and not in common with hUCP3 and Figs. 2a-2d for the mUCP3a nucleic acid domains in common (bold) and not in common with the nucleic acid domains of hUCP3.

The subject domains provide mUCP3 domain specific activity or function which are conveniently determined *in vitro,* cell-based, or *in vivo* assays: e.g. *in vitro* binding assays, cell culture assays, in animals (e.g. gene therapy, transgenics, etc.), etc. mUCP3-binding specificity may assayed by binding equilibrium constants (usually at least about $10^7 M^{-1}$, preferably at least about $10^8 M^{-1}$, more preferably at least about $10^9 M^{-1}$), by the ability of the subject polypeptide to function as negative mutants in mUCP3-expressing cells, to elicit mUCP3 specific antibody in a heterologous host (e.g a rabbit), etc. In any event, the mUCP3 binding specificity of the subject mUCP3 polypeptides necessarily distinguishes that of hUCP3. Preferred peptides demonstrate mUCP3 domain specific activity as assayed by respiratory uncoupling activity, ATP-binding or binding inhibitory activity, mUCP3-specific antibody binding, etc. For example, mUCP3 domain peptides with assay demonstrable mUCP3 domain-specific activities include: SEQ ID NO:2, residues 3-12; SEQ ID NO:2, residues 37-58; SEQ ID NO:2, residues 100-115; SEQ ID NO:2, residues 144-158; SEQ ID NO:2, residues 182-198; SEQ ID NO:2, residues 198-209 SEQ ID NO:2, residues 242-266; SEQ ID NO:2, residues 268-290; and SEQ ID NO:2, residues 297-308.

The subject mUCP3 polypeptides are isolated or pure: an "isolated" polypeptide is unaccompanied by at least some of the material with which it is associated in its natural state, preferably constituting at least about 0.5%, and more preferably at least about 5% by weight of the total polypeptide in a given sample and a pure polypeptide constitutes at least about 90%, and preferably at least about 99% by weight of the total polypeptide in a given sample. A polypeptide, as used herein, is an polymer of amino acids, generally at least 6 residues, preferably at least about 10 residues, more preferably at least about 25 residues, most preferably at least about 50 residues in length. The mUCP3 polypeptides and polypeptide domains may be synthesized, produced by recombinant technology, or purified from mammalian, preferably murine cells. A wide variety of molecular and biochemical methods are available for biochemical synthesis, molecular expression and purification of the subject compositions, see e.g. Molecular Cloning, A Laboratory Manual (Sambrook, *et al.* Cold Spring Harbor Laboratory), Current Protocols in Molecular Biology (Eds. Ausubel, *et al.*, Greene Publ. Assoc., Wiley-Interscience, NY) or that are otherwise known in the art.

For example, the invention provides a method of making a polypeptide comprising

the steps of introducing an isolated or recombinant nucleic acid encoding a subject polypeptide into a host cell or cellular extract, incubating said host cell or extract under conditions whereby said nucleic acid is expressed as a transcript and said transcript is expressed as a translation product comprising said polypeptide, and isolating said translation product.

The invention provides binding agents specific to the claimed mUCP3 polypeptides, including substrates, agonists, antagonists, natural intracellular binding targets, etc., methods of identifying and making such agents, and their use in pharmaceutical development. Novel mUCP3-specific binding agents include mUCP3-specific receptors, such as somatically recombined polypeptide receptors like specific antibodies or T-cell antigen receptors (see, e.g Harlow and Lane (1988) Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory) and other natural intracellular binding agents identified with assays such as one-, two- and three-hybrid screens. non-natural intracellular binding agents identified in screens of chemical libraries such as described below, etc. Agents of particular interest modulate mUCP3 function, e.g. mUCP3-dependent respiratory coupling.

Accordingly, the invention provides methods for modulating respiration involving an mUCP3 gene product comprising the step of modulating mUCP3 activity, e.g. by contacting the cell with an mUCP3-specific binding agent. The cell may reside in culture or in situ, i.e. within the natural host. Preferred inhibitors are orally active in mammalian hosts. For diagnostic uses, the inhibitors or other mUCP3 binding agents are frequently labeled, such as with fluorescent, radioactive, chemiluminescent, or other easily detectable molecules, either conjugated directly to the binding agent or conjugated to a probe specific for the binding agent.

The amino acid sequences of the disclosed mUCP3 polypeptides are used to back-translate mUCP3 polypeptide-encoding nucleic acids optimized for selected expression systems (Holler et al. (1993) Gene 136, 323-328; Martin et al. (1995) Gene 154, 150-166) or used to generate degenerate oligonucleotide primers and probes for use in the isolation of natural mUCP3-encoding nucleic acid sequences ("GCG" software, Genetics Computer Group, Inc, Madison WI). mUCP3-encoding nucleic acids used in mUCP3-expression vectors and incorporated into recombinant host cells, e.g. for expression and screening, transgenic animals, e.g. for functional studies such as the efficacy of candidate drugs for

disease associated with mUCP3-modulated cell function, etc.

The invention also provides nucleic acid hybridization probes, knockin/out constructs and replication / amplification primers having a mUCP3 cDNA specific sequence comprising SEQ ID NOS:1, 3 and 5, or fragments thereof, and sufficient to effect specific hybridization thereto (i.e. specifically hybridize with SEQ ID NOS:1, 3 and 5 in the presence of the UCP1, UCP2 and hUCP3 cDNA. Such primers or probes are at least 12, preferably at least 24, more preferably at least 36 and most preferably at least 96 bases in length. Demonstrating specific hybridization generally requires stringent conditions, for example, hybridizing in a buffer comprising 30% formamide in 5 x SSPE (0.18 M NaCl, 0.01 M $NaPO_4$, pH7.7, 0.001 M EDTA) buffer at a temperature of 42°C and remaining bound when subject to washing at 42°C with 0.2 x SSPE; preferably hybridizing in a buffer comprising 50% formamide in 5 x SSPE buffer at a temperature of 42°C and remaining bound when subject to washing at 42°C with 0.2 x SSPE buffer at 42°C. mUCP3 nucleic acids can also be distinguished using alignment algorithms. such as BLASTX (Altschul *et al.* (1990) Basic Local Alignment Search Tool, J Mol Biol 215, 403-410).

The subject nucleic acids are of synthetic/non-natural sequences and/or are isolated, i.e. unaccompanied by at least some of the material with which it is associated in its natural state, preferably constituting at least about 0.5%, preferably at least about 5% by weight of total nucleic acid present in a given fraction, and usually recombinant, meaning they comprise a non-natural sequence or a natural sequence joined to nucleotide(s) other than that which it is joined to on a natural chromosome. Recombinant nucleic acids comprising the nucleotide sequence of SEQ ID NOS:1, 3 and 5, or fragments thereof contain such sequence or fragment at a terminus, immediately flanked by (i.e. contiguous with) a sequence other than that which it is joined to on a natural chromosome, or flanked by a native flanking region fewer than 10 kb, preferably fewer than 2 kb, which is at a terminus or is immediately flanked by a sequence other than that which it is joined to on a natural chromosome. While the nucleic acids are usually RNA or DNA, it is often advantageous to use nucleic acids comprising other bases or nucleotide analogs to provide modified stability, etc.

The subject nucleic acids find a wide variety of applications including use as translatable transcripts, hybridization probes, PCR primers, diagnostic nucleic acids,

knockin/out constructsetc.; use in detecting the presence of mUCP3 genes and gene transcripts and in detecting or amplifying nucleic acids encoding additional mUCP3 homologs and structural analogs. In diagnosis, mUCP3 hybridization probes find use in identifying wild-type and mutant mUCP3 alleles in clinical and laboratory samples. In a particular embodiment, mUCP3 nucleic acids are used to modulate cellular expression or intracellular concentration or availability of active mUCP3 by binding and/or recombining with an endogenous mUCP3 gene or gene transcript. Methods for effecting anti-sense hyridization, homologous and non-homologous recombinations, and generating transgenic animals and cell lines are well-established in the art.

The following experimental section and examples are offered by way of illustration and not by way of limitation.

EXAMPLES

1. Cloning of mUCP3 cDNAs

We searched murine EST databases using human UCP2 cDNA sequence to identify a cDNA with sequence similarity to known human and mouse UCP2 cDNA sequences. Isolated, cloning and sequencing of this clone revealed a novel gene designated mUCP3, with greatest sequence similarity to a human UCP3 gene. Since the clone lacked the 5' end UTR and part of the coding sequence, we designed a primer for 5' end RACE of the cDNA sequence using mouse skeletal muscle cDNA (PCR condition: 95 0C, 40 sec, 55 0C 2 min, 72 0C, 3 min for 30 cycles). Several clones from the RACE PCR contain sequences that overlap with the partial cDNA sequence. A EcoRI tagged forward primer and XbaI tagged reverse primer were used to amplify the full mUCP3 cDNA using mouse skeletal muscle cDNA. A 2.8 kb mUCP3 cDNA was amplified and cloned into pBlue-Script SK. Several smaller fragments (1.5-2 kb) detected in the PCR products in lesser quantities were also cloned and DNA sequencing confirmed that they were alternatively spliced forms of mUCP3 cDNA.

The largest mUCP3 cDNA (mUCP3a) is 2,782 bp long, containing 239 bp 5' end untranslated region, a 816 bp ORF and 1.7 kb 3' end UTR. The mRNA transcript is about 2.8 kb and the translation product contains 308 amino acid residues. It is 85% identical to the hUCP3 and 73% and 54% identical to mUCP2 and mUCP1, respectively, indicating a similar functional roles in uncoupling mitochondrial respiration. Two shorter isoforms,

mUCP3b and mUCP3c are 1,949 bp and 1,777 bp, with translation products of 432 and 256 amino acid residues respectively (see, Fig. 3).

2. Expression of mUCP3 cDNAs

Because of the extensive DNA sequence homology between our mUCP3 genes and mUCP2, we designed a set of primers designed for PCR amplification of a 335 bp mUCP3 specific DNA sequence and cloned into pBlue-Script SK. The cloned fragment was labeled through reverse transcription using a T3/T7 Reverse Transcription Kit from Ambion and used as a probe for Northern blot analysis of mUCP3 expression. The mouse multiple tissue blots were purchased from Clontech and Northern analysis was performed using a Northern Max kit purchased from Ambion. Northern analysis revealed specific enhanced expression in heart and especially skeletal muscle tissues as compared with negligble expression in brain, spleen, lung, liver, kidney and testis tissues.

3. Protocol for high throughput mUCP3a - antibody binding assay.

A. Reagents:

- Neutralite Avidin: 20 µg/ml in PBS.

- Blocking buffer: 5% BSA, 0.5% Tween 20 in PBS; 1 hour at room temperature.

- Assay Buffer: 100 mM KCl, 20 mM HEPES pH 7.6, 1 mM $MgCl_2$, 1% glycerol, 0.5% NP-40, 50 mM b-mercaptoethanol, 1 mg/ml BSA, cocktail of protease inhibitors.

- ^{33}P mUCP3a polypeptide 10x stock: 10^{-8} - 10^{-6} M "cold" mUCP3 supplemented with 200,000-250,000 cpm of labeled mUCP3a (Beckman counter). Place in the 4°C microfridge during screening.

- Protease inhibitor cocktail (1000X): 10 mg Trypsin Inhibitor (BMB # 109894), 10 mg Aprotinin (BMB # 236624), 25 mg Benzamidine (Sigma # B-6506), 25 mg Leupeptin (BMB # 1017128), 10 mg APMSF (BMB # 917575), and 2mM $NaVO_3$ (Sigma # S-6508) in 10 ml of PBS.

-mUCP3-specific antibody: 10^{-7} - 10^{-5} M biotinylated antibody in PBS.

B. Preparation of assay plates:

- Coat with 120 µl of stock N-Avidin per well overnight at 4°C.

- Wash 2 times with 200 µl PBS.

- Block with 150 µl of blocking buffer.

- Wash 2 times with 200 µl PBS.

C. Assay:

- Add 40 µl assay buffer/well.

- Add 10 µl compound or extract.

- Add 10 µl ^{33}P-mUCP3a (20-25,000 cpm/0.1-10 pmoles/well =10^{-9}- 10^{-7} M final conc).

- Shake at 25°C for 15 minutes.

- Incubate additional 45 minutes at 25°C.

- Add 40 µM biotinylated antibody (0.1-10 pmoles/40 ul in assay buffer)

- Incubate 1 hour at room temperature.

- Stop the reaction by washing 4 times with 200 µM PBS.

- Add 150 µM scintillation cocktail.

- Count in Topcount.

D. Controls for all assays (located on each plate):

a. Non-specific binding

b. Soluble (non-biotinylated antibody) at 80% inhibition.

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Zhang, Ning
Amaral, M. Catherine
Chen, Jin-Long

(ii) TITLE OF INVENTION: UCP3 Genes

(iii) NUMBER OF SEQUENCES: 6

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(B) STREET: 75 DENISE DRIVE
(C) CITY: HILLSBOROUGH
(D) STATE: CALIFORNIA
(E) COUNTRY: USA
(F) ZIP: 94010

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: OSMAN, RICHARD A
(B) REGISTRATION NUMBER: 36,627
(C) REFERENCE/DOCKET NUMBER: T97-009

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: (650) 343-4341
(B) TELEFAX: (650) 343-4342

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2782 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

GTCAGCTGGT GCACAGGGCC AGTGCCGAGC CAGGGACAGC AGAGACAACA GTGAATGGTG 60
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CAAGCTCTCT CCTCGGACCT CCATAGGCAG CAAAGGAACC AGGCCCATTC CCCGGGACCA 240
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CCATCCTGAC TATGGTGCGC ACAGAGGGTC CCCGCAGCCC CTACAGCGGA CTGGTCGCTG 480
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AAAAAAAAAA AAAAAAAAAA AA 2782

(2) INFORMATION FOR SEQ ID NO:2:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 308 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

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Phe Leu Gly Ala Gly Thr Ala Ala Cys Phe Ala Asp Leu Leu Thr Phe
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Pro Leu Asp Thr Ala Lys Val Arg Leu Gln Ile Gln Gly Glu Asn Pro
35 40 45
Gly Ala Gln Ser Val Gln Tyr Arg Gly Val Leu Gly Thr Ile Leu Thr
50 55 60
Met Val Arg Thr Glu Gly Pro Arg Ser Pro Tyr Ser Gly Leu Val Ala
65 70 75 80
Gly Leu His Arg Gln Met Ser Phe Ala Ser Ile Arg Ile Gly Leu Tyr
85 90 95
Asp Ser Val Lys Gln Phe Tyr Thr Pro Lys Gly Ala Asp His Ser Ser
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Gly Thr Trp Pro Asn Ile Thr Arg Asn Ala Ile Val Asn Cys Ala Glu
            180                 185                 190
Met Val Thr Tyr Asp Ile Ile Lys Glu Lys Leu Leu Glu Ser His Leu
        195                 200                 205
Phe Thr Asp Asn Phe Pro Cys His Phe Val Ser Ala Phe Gly Ala Gly
    210                 215                 220
Phe Cys Ala Thr Val Val Ala Ser Pro Val Asp Val Val Lys Thr Arg
225                 230                 235                 240
Tyr Met Asn Ala Pro Leu Gly Arg Tyr Arg Ser Pro Leu His Cys Met
                245                 250                 255
Leu Lys Met Ala Ala Gln Glu Gly Pro Thr Ala Phe Tyr Lys Gly Phe
            260                 265                 270
Val Pro Ser Phe Leu Arg Leu Gly Ala Trp Asn Val Met Met Phe Val
        275                 280                 285
Thr Tyr Glu Gln Leu Lys Arg Ala Leu Met Lys Val Gln Val Leu Arg
    290                 295                 300
Glu Ser Pro Phe
305
```

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1949 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

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

```
GTCAGCTGGT GCACAGGGCC AGTGCCGAGC CAGGGACAGC AGAGACAACA GTGAATGGTG      60
AGGCCCGGCC GTCAGATCCT GCTGCTACCT AATGGAGTGG AGCCTTAGGG TGGCCCTGCA     120
CTACCCAACC TTGGCTAGAC GCACAGCTTC CTCCCTGAAC TGAAGCAAAA GATTGCCAGG     180
CAAGCTCTCT CCTCGGACCT CCATAGGCAG CAAAGGAACC AGGCCCATTC CCCGGGACCA     240
TGGTTGGACT TCAGCCCTCC GAAGTGCCTC CCACAACGGT TGTGAAGTTC CTGGGGGCCG     300
GCACTGCGGC CTGTTTTGCG GACCTCCTCA CTTTTCCCCT GGACACCGCC AAGGTCCGTC     360
TGCAGATCCA AGGGGAGAAC CCAGGGGCTC AGAGCGTGCA GTACCGCGGT GTGCTGGGTA     420
CCATCCTGAC TATGGTGCGC ACAGAGGGTC CCCGCAGCCC CTACAGCGGA CTGGTCGCTG     480
GCCTGCACCG CCAGATGAGT TTTGCCTCCA TTCGAATTGG CCTCTACGAC TCTGTCAAGC     540
AGTTCTACAC CCCCAAGGGA GCGGACCACT CCAGCGTCGC CATCAGGATT CTGGCAGGCT     600
GCACGACAGG AGCCATGGCA GTGACCTGCG CCCAGCCCAC GGATGTGGTG AAGGTCCGAT     660
TTCAAGCCAT GATACGCCTG GGAACTGGAG GAGAGAGGAA ATACAGAGGG ACTATGGATG     720
CCTACAGAAC CATCGCCAGG GAGGAAGGAG TCAGGGGCCT GTGGAAAGGG ACTTGGCCCA     780
ACATCACAAG AAATGCCATT GTCAACTGTG CTGAGATGGT GACCTACGAC ATCATCAAGG     840
AGAAGTTGCT GGAGTCTCAC CTGTTTACTG ACAACTTCCC CTGTCACTTT GTCTCTGCCT     900
TTGGAGCTGG CTTCTGTGCC ACAGTGGTGG CCTCCCCGGT GGATGTGGTA AAGACCCGAT     960
ACATGAACGC TCCCCTAGGC AGGTACCGCA GCCCTCTGCA CTGTATGCTG AAGATGGTGG    1020
CTCAGGAGGG ACCCACGGCC TTCTACAAAG GATTTGTGCC CTCCTTTCTG CGTCTGGGAG    1080
CTTGGAACGT GATGATGTTT GTAACATATG AGCAACTGAA GAGGGCCTTA ATGAAAGTCC    1140
AGGGTGTTGG GAAGATAGAA AGCGAAGCAG ACATGGAAGC ACTTCCTAAC AAGGCCTGTC    1200
ATCGTCATCA TCTACAAATG GCAAGAACGA GAACAGCTGC TCTTCTGCCC TCTCTCTCGG    1260
AGGTTTTCTC ATCTCAGGGT CCTACCTGCC AGGCTCCTGA CCAGCTCCAC CTGCCCACAC    1320
TTCCTCCTGC TCTCGCTGCC TTTGGCTGCA GAGCCTTTGC TCCTCCTGTT AAGCCTTCAG    1380
TCTTCCATCT GCAAAAGGGA GGGCAAAGCA CAGGACCAAC TTCCAAGCTT AAAAATGCAC    1440
ATCTGACAAC AAAATGGCTC AGTGGGGTCC ATTCATGGGA CCCACATGGT GGAAGGACAG    1500
AATGGACTCT TGCAAATTGT CCTCTGACCT CCATTTGAGC GCCCTATACA TGTGACTGTA    1560
CATATGTACA AACACGATAA AGATGGAAAC ACATGTAAAA ACATAAAAAT AAAAAGTTGT    1620
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ACTGGATGTG GTGGTTTGAA TGAGATGTTC CTCGTGTCTC GGGCATTTGA AGACTTGCTC 1680
CCCAGTTGTT GGCGGCTGTT TGGGGAGGCT TAGAAGATGT GGCCTTTTGG GAAGCAGGGT 1740
GTCATTGAGG ACTGGCTTGG AGAGCCTAAA GATCCGAGGC ACTCCCAGTT TCTCTGGTTT 1800
TTCATTTTGA GGTGTGAGGT CTTATTGGCT GCACCAGTCT CCATGCCTGT CTGTTGCCCG 1860
GCCTCCTCAC CATGATGGAC TTTTATCTCT CTGTACTTGT AAGCCCCAAA TAAACCTTCC 1920
ATCTGTGAAA AAAAAAAAAA AAAAAAAAA 1949

(2) INFORMATION FOR SEQ ID NO:4:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 432 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Met Val Gly Leu Gln Pro Ser Glu Val Pro Pro Thr Thr Val Val Lys
1 5 10 15
Phe Leu Gly Ala Gly Thr Ala Ala Cys Phe Ala Asp Leu Leu Thr Phe
20 25 30
Pro Leu Asp Thr Ala Lys Val Arg Leu Gln Ile Gln Gly Glu Asn Pro
35 40 45
Gly Ala Gln Ser Val Gln Tyr Arg Gly Val Leu Gly Thr Ile Leu Thr
50 55 60
Met Val Arg Thr Glu Gly Pro Arg Ser Pro Tyr Ser Gly Leu Val Ala
65 70 75 80
Gly Leu His Arg Gln Met Ser Phe Ala Ser Ile Arg Ile Gly Leu Tyr
85 90 95
Asp Ser Val Lys Gln Phe Tyr Thr Pro Lys Gly Ala Asp His Ser Ser
100 105 110
Val Ala Ile Arg Ile Leu Ala Gly Cys Thr Thr Gly Ala Met Ala Val
115 120 125
Thr Cys Ala Gln Pro Thr Asp Val Val Lys Val Arg Phe Gln Ala Met
130 135 140
Ile Arg Leu Gly Thr Gly Gly Glu Arg Lys Tyr Arg Gly Thr Met Asp
145 150 155 160
Ala Tyr Arg Thr Ile Ala Arg Glu Glu Gly Val Arg Gly Leu Trp Lys
165 170 175
Gly Thr Trp Pro Asn Ile Thr Arg Asn Ala Ile Val Asn Cys Ala Glu
180 185 190
Met Val Thr Tyr Asp Ile Ile Lys Glu Lys Leu Leu Glu Ser His Leu
195 200 205
Phe Thr Asp Asn Phe Pro Cys His Phe Val Ser Ala Phe Gly Ala Gly
210 215 220
Phe Cys Ala Thr Val Val Ala Ser Pro Val Asp Val Val Lys Thr Arg
225 230 235 240
Tyr Met Asn Ala Pro Leu Gly Arg Tyr Arg Ser Pro Leu His Cys Met
245 250 255
Leu Lys Met Val Ala Gln Glu Gly Pro Thr Ala Phe Tyr Lys Gly Phe
260 265 270
Val Pro Ser Phe Leu Arg Leu Gly Ala Trp Asn Val Met Met Phe Val
275 280 285
Thr Tyr Glu Gln Leu Lys Arg Ala Leu Met Lys Val Gln Gly Val Gly
290 295 300
Lys Ile Glu Ser Glu Ala Asp Met Glu Ala Leu Pro Asn Lys Ala Cys
305 310 315 320
His Arg His His Leu Gln Met Ala Arg Thr Arg Thr Ala Ala Leu Leu
325 330 335

Pro Ser Leu Ser Glu Val Phe Ser Ser Gln Gly Pro Thr Cys Gln Ala
340 345 350
Pro Asp Gln Leu His Leu Pro Thr Leu Pro Pro Ala Leu Ala Ala Phe
355 360 365
Gly Cys Arg Ala Phe Ala Pro Pro Val Lys Pro Ser Val Phe His Leu
370 375 380
Gln Lys Gly Gly Gln Ser Thr Gly Pro Thr Ser Lys Leu Lys Asn Ala
385 390 395 400
His Leu Thr Thr Lys Trp Leu Ser Gly Val His Ser Trp Asp Pro His
405 410 415
Gly Gly Arg Thr Glu Trp Thr Leu Ala Asn Cys Pro Leu Thr Ser Ile
420 425 430

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1777 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: double

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

GTCAGCTGGT GCACAGGGCC AGTGCCGAGC CAGGGACAGC AGAGACAACA GTGAATGGTG 60
AGGCCCGGCC GTCAGATCCT GCTGCTACCT AATGGAGTGG AGCCTTAGGG TGGCCCTGCA 120
CTACCCAACC TTGGCTAGAC GCACAGCTTC CTCCCTGAAC TGAAGCAAAA GATTGCCAGG 180
CAAGCTCTCT CCTCGGACCT CCATAGGCAG CAAAGGAACC AGGCCCATTC CCCGGGACCA 240
TGGTTGGACT TCAGCCCTCC GAAGTGCCTC CCACAACGGT TGTGAAGTTC CTGGGGGCCG 300
GCACTGCGGC CTGTTTTGCG GACCTCCTCA CTTTTCCCCT GGACACCGCC AAGGTCCGTC 360
TGCAGATCCA AGGGGAGAAC CCAGGGGCTC AGAGCGTGCA GTACCGCGGT GTGCTGGGTA 420
CCATCCTGAC TATGGTGCGC ACAGAGGGTC CCCGCAGCCC CTACAGCGGA CTGGTCGCTG 480
GCCTGCACCG CCAGATGAGT TTTGCCTCCA TTCGAATTGG CCTCTACGAC TCTGTCAAGC 540
AGTTCTACAC CCCCAAGGGA GCGGACCACT CCAGCGTCGC CATCAGGATT CTGGCAGGCT 600
GCACGACAGG AGCCATGGCA GTGACCTGCG CCCAGCCCAC GGATGTGGTG AAGGTCCGAT 660
TTCAAGCCAT GATACGCCTG GGAACTGGAG GAGAGAGGAA ATACAGAGGG ACTATGGATG 720
CCTACAGAAC CATCGCCAGG GAGGAAGGAG TCAGGGGCCT GTGGAAAGGG ACTTGGCCCA 780
ACATCACAAG AAATGCCATT GTCAACTGTG CTGAGATGGT GACCTACGAC ATCATCAAGG 840
AGAAGTTGCT GGAGTCTCAC CTGTTTACTG ACAACTTCCC CTGTCACTTT GTCTCTGCCT 900
TTGGAGCTGG CTTCTGTGCC ACAGTGGTGG CCTCCCCGGT GGATGTGGTA AAGACCCGAT 960
ACATGAACGC TCCCCTAGGC AGGTACCGCA GCAGGACTCA GAATCTTTAG GGAATTGTTA 1020
GGACTGGTAA AAGAATTTCC ACCTTAGGGC AAGAACGAGA ACAGCTGCTC TTCTGCCTTC 1080
TCTCTCGGAG GTTTTCTCAT CTCAGGGTCC TACCTGCCAG GCTCCTGACC AGCTCCACCT 1140
GCCCACACTT CCTCCTGCTC TCGCTGCCTT TGGCTGCAGA GCCTTTGCTC CTCCTGTTAA 1200
GCCTTCAGTC TTCCATCTGC AAAAGGGAGG GCAAAGCACA GGACCAACTT CCAAGCTTAA 1260
AAATGCACAT CTGACAACAA AATGGCTCAG TGGGGTCCAT TCATGGGACC CACATGGTGG 1320
AAGGACAGAA TGGACTCTTG CAAATTGTCC TCTGACCTCC ATTTGAGCGC CCTATACATG 1380
TGACTGTACA TATGTACAAA CACGATAAAG ATGGAAACAC ATGTAAAAAC ATAAAAATAA 1440
AAAGTTGTAC TGGATGTGGT GGTTTGAATG AGATGTTCCT CGTGTCTCGG GCATTTGAAG 1500
ACTTGCTCCC CAGTTGTTGG CGGCTGTTTG GGGAGGCTTA GAAGATGTGG CCTTTTGGGA 1560
AGCAGGGTGT CATTGAGGAC TGGCTTGGAG AGCCTAAAGA TCCGAGGCAC TCCCAGTTTC 1620
TCTGGTTTTT CATTTTGAGG TGTGAGGTCT TATTGGCTGC ACCAGTCTCC ATGCCTGTCT 1680
GTTGCCCGGC CTCCTCACCA TGATGGACTT TTATCTCTCT GTACTTGTAA GCCCCAAATA 1740
AACCTTCCAT CTGTGAAAAA AAAAAAAAAA AAAAAAA 1777

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 256 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

```
Met Val Gly Leu Gln Pro Ser Glu Val Pro Pro Thr Thr Val Val Lys
1               5                  10                  15
Phe Leu Gly Ala Gly Thr Ala Ala Cys Phe Ala Asp Leu Leu Thr Phe
            20                  25                  30
Pro Leu Asp Thr Ala Lys Val Arg Leu Gln Ile Gln Gly Glu Asn Pro
        35                  40                  45
Gly Ala Gln Ser Val Gln Tyr Arg Gly Val Leu Gly Thr Ile Leu Thr
    50                  55                  60
Met Val Arg Thr Glu Gly Pro Arg Ser Pro Tyr Ser Gly Leu Val Ala
65                  70                  75                  80
Gly Leu His Arg Gln Met Ser Phe Ala Ser Ile Arg Ile Gly Leu Tyr
                85                  90                  95
Asp Ser Val Lys Gln Phe Tyr Thr Pro Lys Gly Ala Asp His Ser Ser
            100                 105                 110
Val Ala Ile Arg Ile Leu Ala Gly Cys Thr Thr Gly Ala Met Ala Val
        115                 120                 125
Thr Cys Ala Gln Pro Thr Asp Val Val Lys Val Arg Phe Gln Ala Met
    130                 135                 140
Ile Arg Leu Gly Thr Gly Gly Glu Arg Lys Tyr Arg Gly Thr Met Asp
145                 150                 155                 160
Ala Tyr Arg Thr Ile Ala Arg Glu Glu Gly Val Arg Gly Leu Trp Lys
                165                 170                 175
Gly Thr Trp Pro Asn Ile Thr Arg Asn Ala Ile Val Asn Cys Ala Glu
            180                 185                 190
Met Val Thr Tyr Asp Ile Ile Lys Glu Lys Leu Leu Glu Ser His Leu
        195                 200                 205
Phe Thr Asp Asn Phe Pro Cys His Phe Val Ser Ala Phe Gly Ala Gly
    210                 215                 220
Phe Cys Ala Thr Val Val Ala Ser Pro Val Asp Val Val Lys Thr Arg
225                 230                 235                 240
Tyr Met Asn Ala Pro Leu Gly Arg Tyr Arg Ser Arg Thr Gln Asn Leu
                245                 250                 255
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WHAT IS CLAIMED IS:

1. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:2, 4, or 6, or a deletion mutant thereof comprising at least an 8 residue domain thereof not found in natural UCP1, 2 or hUCP3 proteins, wherein said polypeptide has an activity selected from at least one of an mUCP3-specific binding or binding inhibitory activity, an mUCP3 respiratory coupling or uncoupling activity and a mUCP3 specific antigenicity or immunogenicity.

2. The isolated polypeptide of claim 1, comprising at least one of SEQ ID NO:2, residues 3-12; SEQ ID NO:2, residues 37-58; SEQ ID NO:2, residues 100-115; SEQ ID NO:2, residues 144-158; SEQ ID NO:2, residues 182-198; SEQ ID NO:2, residues 198-209 SEQ ID NO:2, residues 242-266; SEQ ID NO:2, residues 268-290; and SEQ ID NO:2, residues 297-308.

3. An isolated or recombinant first nucleic acid comprising a strand of SEQ ID NO:1, 3 or 5 or at least 24 consecutive bases thereof and sufficient to specifically hybridize with a second nucleic acid comprising the opposite corresponding strand of SEQ ID NO:1, 3 or 5, in the presence of UCP1, UCP2 and hUCP3 cDNA.

4. A recombinant nucleic acid encoding a polypeptide according to claim 1.

5. A cell comprising a nucleic acid according to claim 4.

6. An antibody which specifically binds a polypeptide according to claim 1.

7. A method of making an polypeptide said method comprising steps: introducing a nucleic acid according to claim 4 into a host cell or cellular extract, incubating said host cell or extract under conditions whereby said nucleic acid is expressed as a transcript and said transcript is expressed as a translation product comprising said polypeptide, and isolating said translation product.

8. A method of modulating a cell comprising a UCP3 gene, said method comprising

the step of introducing into said cell a first nucleic acid according to claim 3, whereby the function and/or structure of the UCP3 gene is modulated.

9. A method according to claim 8, wherein the nucleic acid is a knock-out or knock-in construct.

10. A cell or progeny of a cell made by the method of claim 9.

CA 02303003 2000-03-06


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MVGLQPSEVPPTTVVKFLGAGTAACFADLLTFPLDTAKVRLQIQGENPGA  50
QSVQYRGVLGTILTMVRTEGPRSPYSGLVAGLHRQMSFASIRIGLYDSVK 100
QFYTPKGADHSSVAIRILAGCTTGAMAVTCAQPTDVVKVRFQAMIRLGTG 150
GERKYRGTMDAYRTIAREEGVRGLWKGTWPNITRNAIVNCAEMVTYDIIK 200
EKLLESHLFTDNFPCHFVSAFGAGFCATVVASPVDVVKTRYMNAPLGRYR 250
SPLHCMLKMAAQEGPTAFYKGFVPSFLRLGAWNVMMFVTYEQLKRALMKV 300
QVLRESPF                                            308
```

Fig 1

GTCAGCTGGT GCACAGGGCC AGTGCCGAGC CAGGGACAGC AGAGACAACA GTGAATGGTG 60

AGGCCCGGCC GTCAGATCCT GCTGCTACCT AATGGAGTGG AGCCTTAGGG TGGCCCTGCA 120

CTACCCAACC TTGGCTAGAC GCACAGCTTC CTCCCTGAAC TGAAGCAAAA GATTGCCAGG 180

CAAGCTCTCT CCTCGGACCT CCATAGGCAG CAAAGGAACC AGGCCCATTC CCCGGGACCA 240

TGGTTGGACT TCAGCCCTCC GAAGTGCCTC CCACAACGGT TGTGAAGTTC CTGGGGGCCG 300

GCACTGCGGC CTGTTTTGCG GACCTCCTCA CTTTTCCCCT GGACACCGCC AAGGTCCGTC 360

TGCAGATCCA AGGGGAGAAC CCAGGGGCTC AGAGCGTGCA GTACCGCGGT GTGCTGGGTA 420

CCATCCTGAC TATGGTGCGC ACAGAGGGTC CCCGCAGCCC CTACAGCGGA CTGGTCGCTG 480

GCCTGCACCG CCAGATGAGT TTTGCCTCCA TTCGAATTGG CCTCTACGAC TCTGTCAAGC 540

AGTTCTACAC CCCCAAGGGA GCGGACCACT CCAGCGTCGC CATCAGGATT CTGGCAGGCT 600

GCACGACAGG AGCCATGGCA GTGACCTGCG CCCAGCCCAC GGATGTGGTG AAGGTCCGAT 660

TTCAAGCCAT GATACGCCTG GGAACTGGAG GAGAGAGGAA ATACAGAGGG ACTATGGATG 720

CCTACAGAAC CATCGCCAGG GAGGAAGGAG TCAGGGGCCT GTGGAAAGGG ACTTGGCCCA 780

Fig 2a

CA 02303003 2000-03-06

ACATCACAAG AAATGCCATT GTCAACTGTG CTGAGATGGT GACCTACGAC ATCATCAAGG 840

AGAAGTTGCT GGAGTCTCAC CTGTTTACTG ACAACTTCCC CTGTCACTTT GTCTCTGCCT 900

TTGGAGCTGG CTTCTGTGCC ACAGTGGTGG CCTCCCCGGT GGATGTGGTA AAGACCCGAT 960

ACATGAACGC TCCCCTAGGC AGGTACCGCA GCCCTCTGCA CTGTATGCTG AAGATGGCGG 1020

CTCAGGAGGG ACCCACGGCC TTCTACAAAG GATTTGTGCC CTCCTTTCTG CGTCTGGGAG 1080

CTTGGAACGT GATGATGTTT GTAACATATG AGCAACTGAA GAGGGCCTTA ATGAAAGTCC 1140

AGGTACTGCG GGAATCTCCG TTTTGAACAA GGCAAGCAGG CTGCCTGAAA CAGAACAAAG 1200

CGTCTCTGCC CTGGGGACAC AGGCCCACAC GGTCCAAAAC CCTGCACTGC TGCTGACACG 1260

AGAAACTGAA CTAAAAGAGG AGAGTTTTAG TCCTCCGTGT TTCGTCCTAA AACACCTCTG 1320

TTTTGCACTG ACCTGATGGG AAATAAATTA TATTAATTTT TAAACCCCTT CCGGTTGGAT 1380

GCCTAATATT TAGGCAAGAG ACAACAAAGA AAACCAGAGT CAACTCCCTT GAAATGTAGG 1440

AATAAAGGAT GCATAATAAA CAGGAAAGGC ACAGGTTTTG AGAAGATCAG CCCACAGTGT 1500

TGTCCTTGAA TCAAACAAAA TGGTCGGAGG AACCCTTCGG CTTCAGCACA AAGAGGTGAC 1560

Fig 2b

TACAGCCTTC TGGTCACCAG ATGACTCCGC CCCTCTGTAA TGAGTCTGCC AAGTAGACTC 1620

TATCAAGATT CTGGGGAAAG GAGAAAGAAC ACATTGATAC TGCACAAATG AGTGGTGCTG 1680

GGCCCACCGA GGACACTGGA GGATGGAGCG TGATCTGGGA TAACAGTCCT TCTCTGTCTG 1740

CCTCATCAGG GTGTTGGGAA GATAGAAAGC GAAGCAGACA TGGAAGCACT TCCTAACAAG 1800

GCCTGTCATC GTCATCATCT ACAAATGTAA GCCTGAGGAC AATGTTTTAG GAGAGATTCT 1860

GTCCAGAGAA GTAGTTTGAG GAAAATGCAG TTTGTAGTGG TAAAGCCATG CACACCTGGA 1920

CTGCATGGTA AGGACCAGGG GTGACGGAAG CCATGGGGAT CCGGTGCCTG GTAACATCAA 1980

AGGGCTGTGG GGGGGGGGGG GCACTGCCTG TCCATCAGTT CAAAGCAGCA GGACTCAGAA 2040

TCTCCACCTT AGGGCAAGAA CGAGAACAGC TGCTCTTCTG CCTTCTCTCT CGGAGGTTTT 2100

CTCATCTCAG GGTCCTACCT GCCAGGCTCC TGACCAGCTC CACCTGCCCA CACTTCCTCC 2160

TGCTCTCGCT GCCTTTGGCT GCAGAGCCTT TGCTCCTCCT GTTAAGCCTT CAGTCTTCCA 2220

TCTGCAAAAG GGAGGGCAAA GCACAGGACC AACTTCCAAG CTTAAAAATG CACATCTGAC 2280

AACAAAATGG CTCAGTGGGG TCCATTCATG GGACCCACAT GGTGGAAGGA CAGAATGGAC 2340

Fig 2c

CA 02303003 2000-03-06

TCTTGCAAAT TGTCCTCTGA CCTCCATTTG AGCGCCCTAT ACATGTGACT GTACATATGT 2400

ACAAACACGA TAAAGATGGA AACACATGTA AAAACATAAA AATAAAAAGT TGTACTGGAT 2460

GTGGTGGTTT GAATGAGATG TTCCTCGTGT CTCGGGCATT TGAAGACTTG CTCCCCAGTT 2520

GTTGGCGGCT GTTTGGGGAG GCTTAGAAGA TGTGGCCTTT TGGGAAGCAG GGTGTCATTG 2580

AGGACTGGCT TGGAGAGCCT AAAGATCCGA GGCACTCCCA GTTTCTCTGG TTTTTCATTT 2640

TGAGGTGTGA GGTCTTATTG GCTGCACCAG TCTCCATGCC TGTCTGTTGC CCGGCCTCCT 2700

CACCATGATG GACTTTTATC TCTCTGTACT TGTAAGCCCC AAATAAACCT TCCATCTGTG 2760

AAAAAAAAAA AAAAAAAAAA AA 2782

Fig 2d

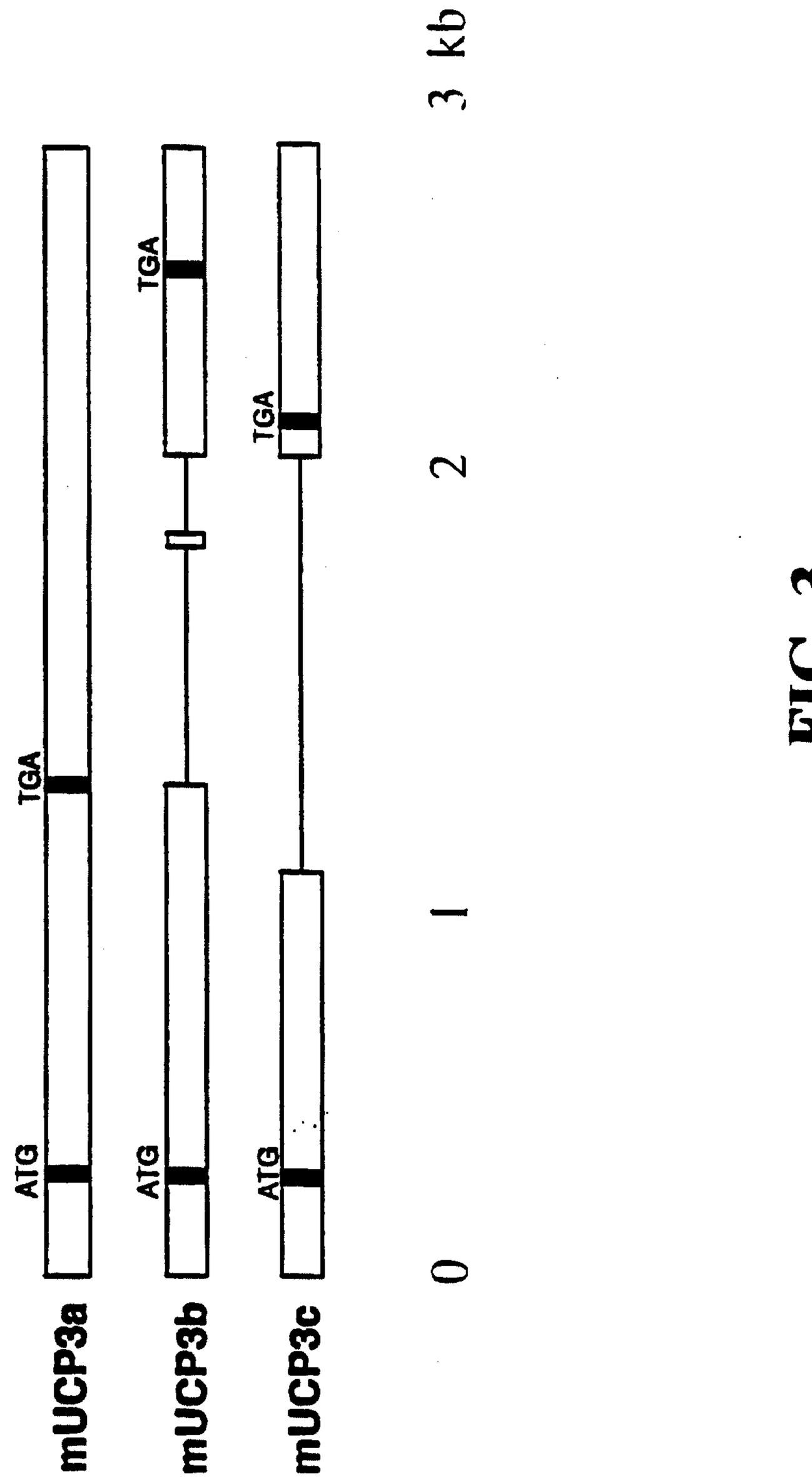

FIG. 3