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Mellor et al.

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(45) **Date of Patent: Jan. 14, 2014**

(54) **SCREENING METHOD FOR CELL AGING**

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(30) **Foreign Application Priority Data**

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(51) **Int. Cl.**
C12Q 1/68 (2006.01)

(52) **U.S. Cl.**
USPC **435/6.11**; 435/375; 435/7.1; 435/7.9; 540/456

(58) **Field of Classification Search**
None
See application file for complete search history.

(56) **References Cited**

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Primary Examiner — Kimberly Chong
(74) *Attorney, Agent, or Firm* — Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd.

(57) **ABSTRACT**

The present invention relates to a method for increasing the chronological lifespan of a cell comprising disrupting the function of at least one of the SAGA1 SLIK and/or SALSA complexes in said cell.

4 Claims, 22 Drawing Sheets

Figure 1

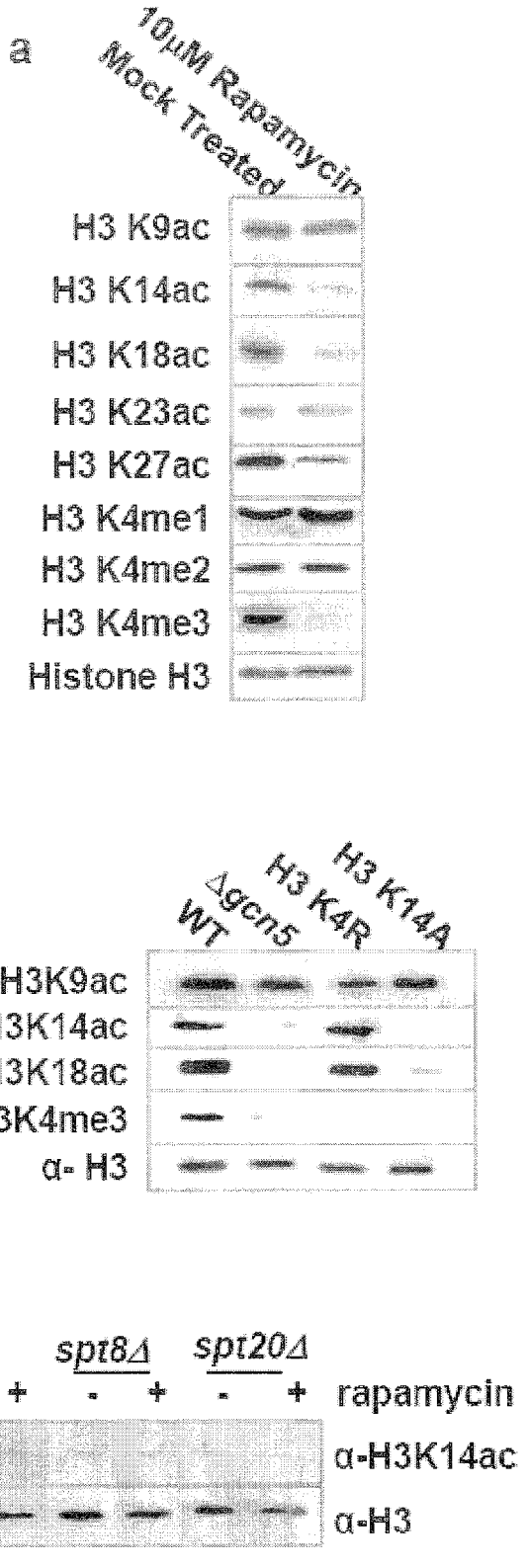

a
Mock Treated
10μM Rapamycin
H3 K9ac
H3 K14ac
H3 K18ac
H3 K23ac
H3 K27ac
H3 K4me1
H3 K4me2
H3 K4me3
Histone H3
b
WT
Δgcn5
H3 K4R
H3 K14A
α-H3K9ac
α-H3K14ac
α-H3K18ac
α-H3K4me3
α- H3
c
WT
spt8Δ
spt20Δ
- + - + - +
rapamycin
α-H3K14ac
α-H3

Figure 1 (cont)

Figure 1 (cont)

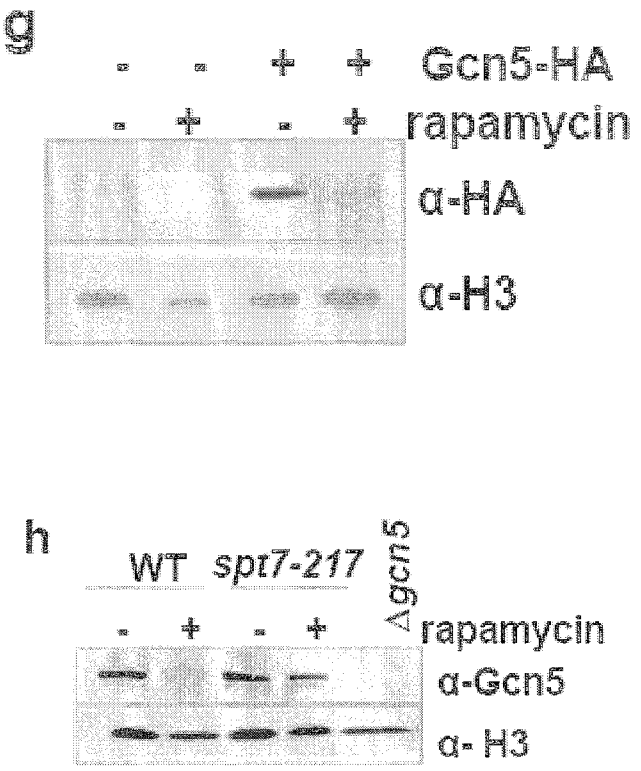


Figure 2

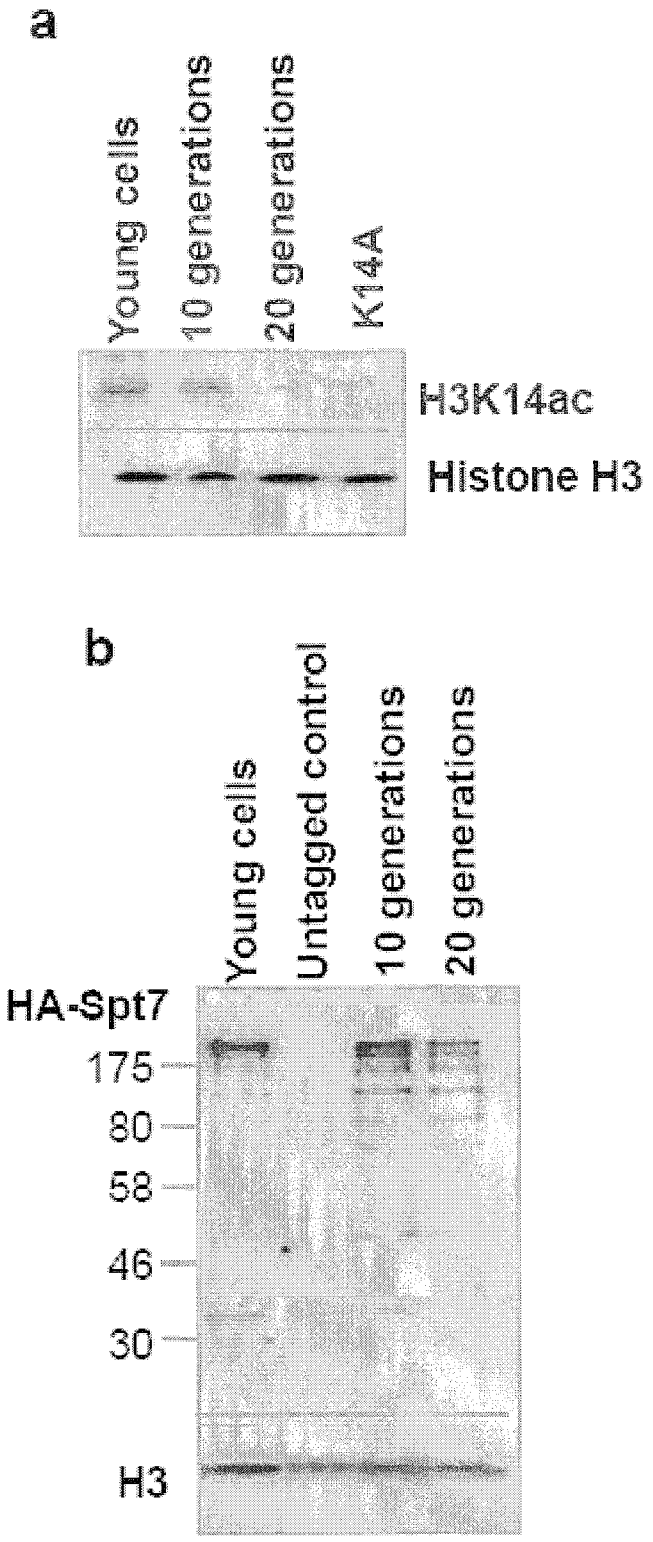

a
Young cells
10 generations
20 generations
K14A
H3K14ac
Histone H3
b
Young cells
Untagged control
10 generations
20 generations
HA-Spt7
175
80
58
46
30
H3

Figure 2 (cont)

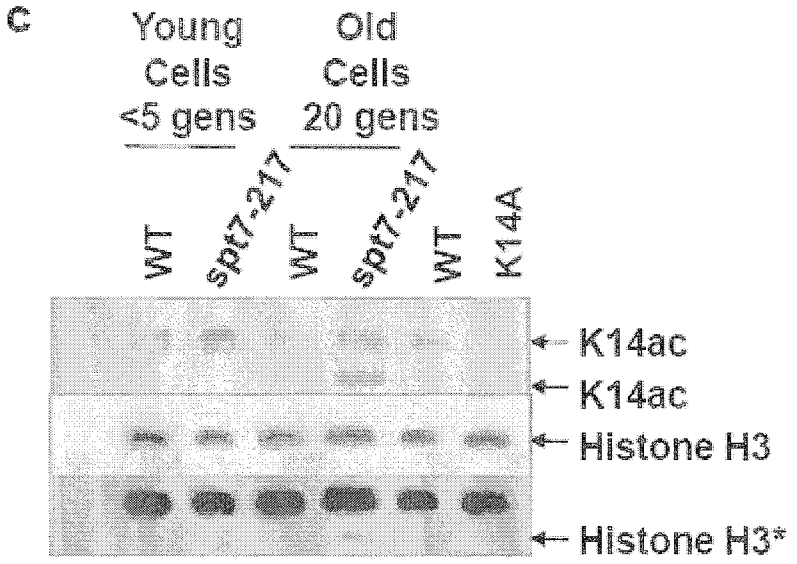


Figure 3

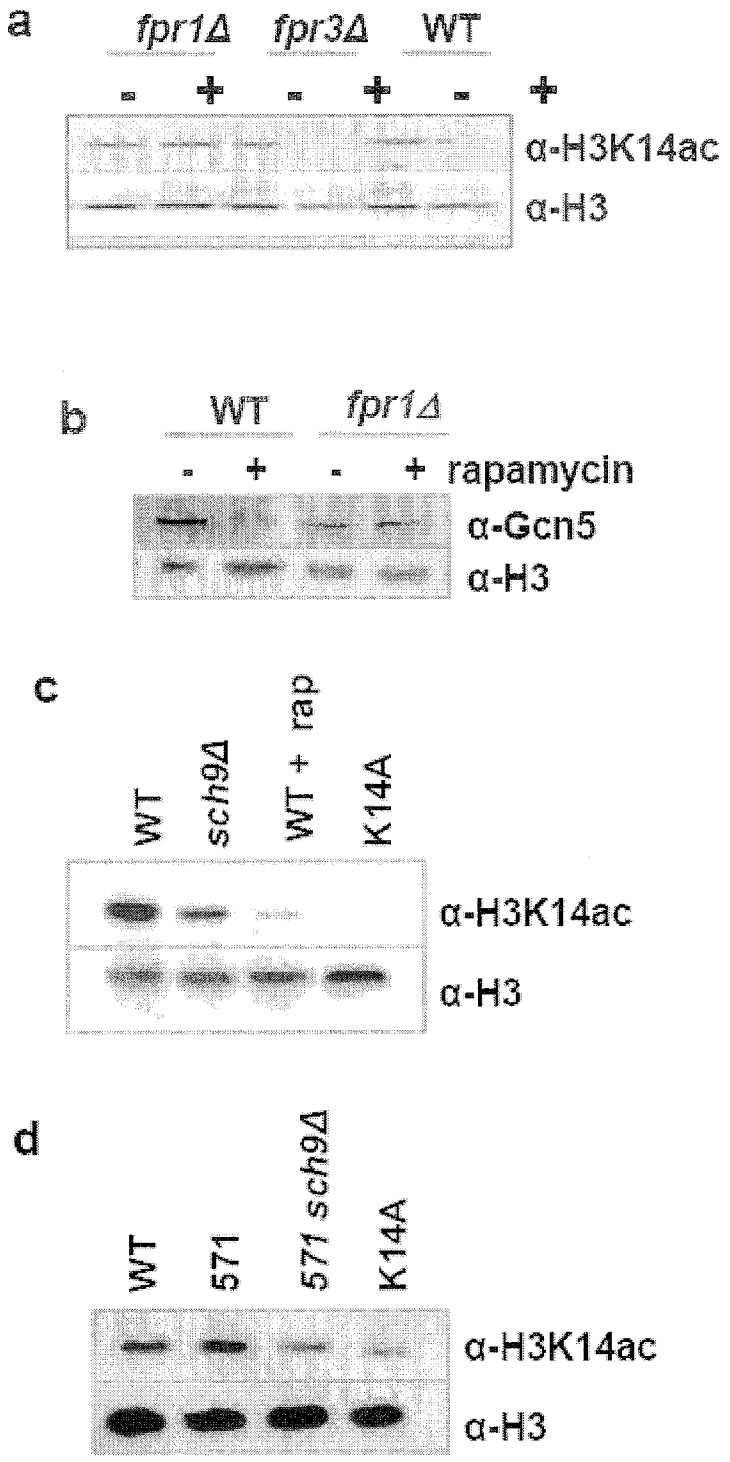

a
fpr1Δ
fpr3Δ
WT
- + - + - +
α-H3K14ac
α-H3
b
WT
fpr1Δ
- + - + rapamycin
α-Gcn5
α-H3
c
WT
sch9Δ
WT + rap
K14A
α-H3K14ac
α-H3
d
WT
571
571 sch9Δ
K14A
α-H3K14ac
α-H3

Figure 3 (cont)

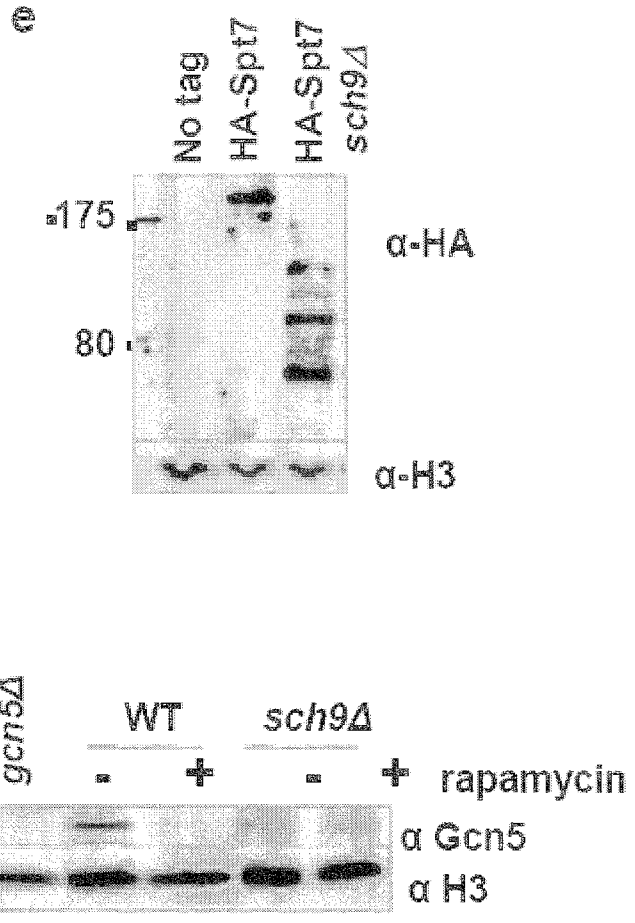
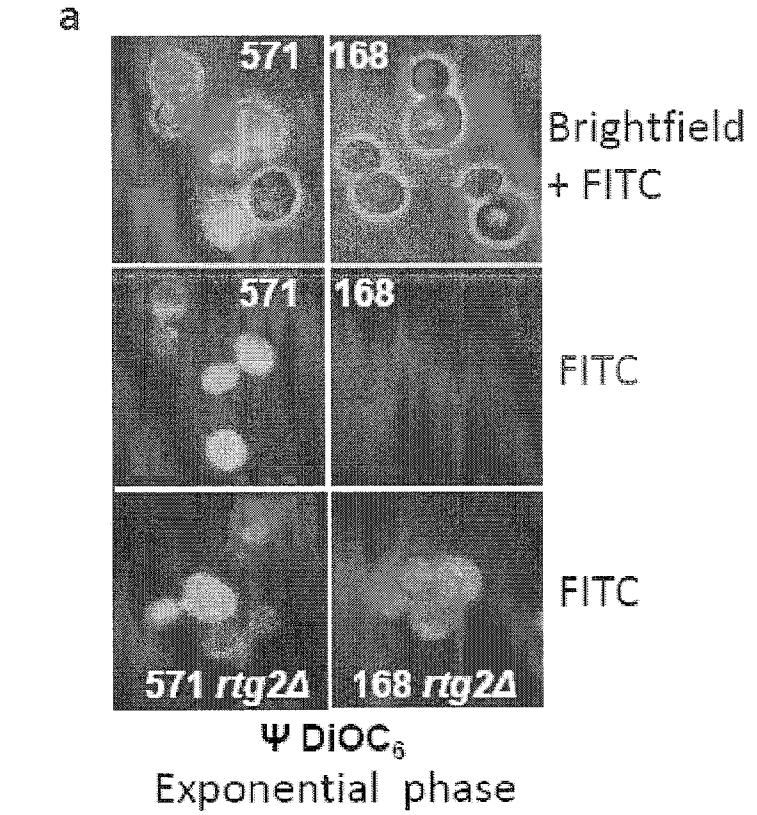


Figure 4


a
571
168
Brightfield
+ FITC
571
168
FITC
571 rtg2Δ
168 rtg2Δ
FITC
Ψ DiOC6
Exponential phase

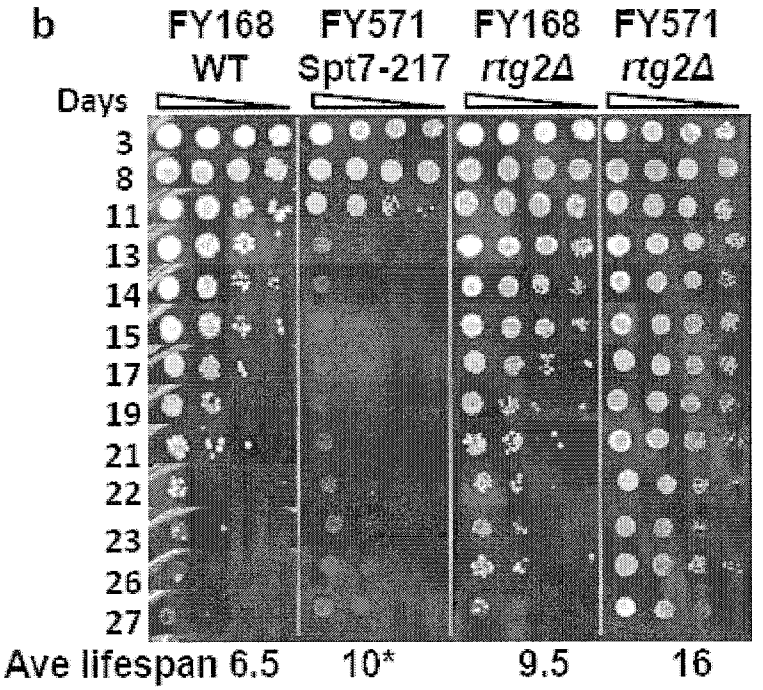

b
FY168
WT
FY571
Spt7-217
FY168
rtg2Δ
FY571
rtg2Δ
Days
3
8
11
13
14
15
17
19
21
22
23
26
27
Ave lifespan 6.5
10*
9.5
16

Figure 4 (cont)

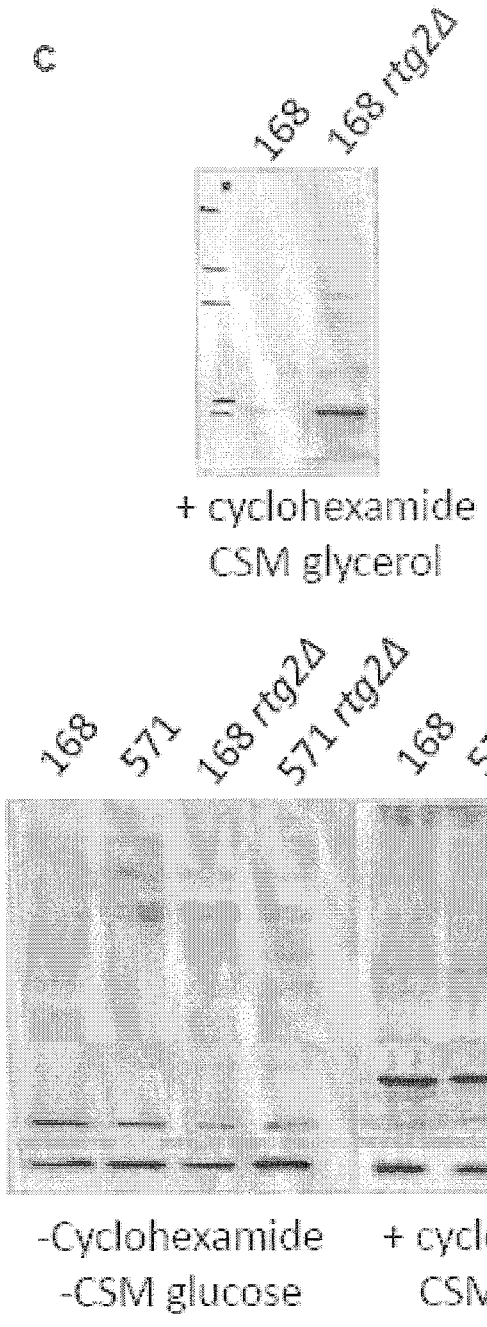


Figure 5

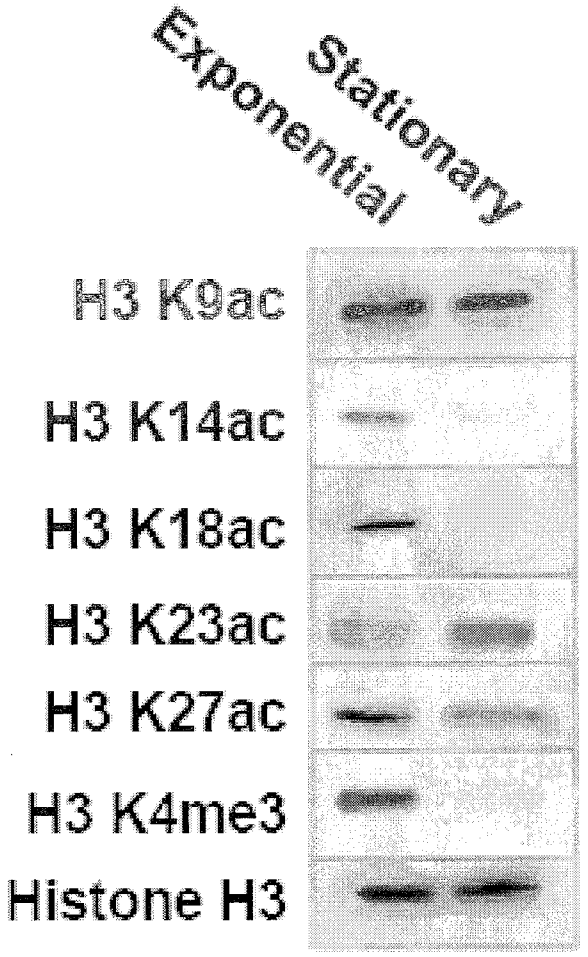

Exponential
Stationary
H3 K9ac
H3 K14ac
H3 K18ac
H3 K23ac
H3 K27ac
H3 K4me3
Histone H3

Figure 6

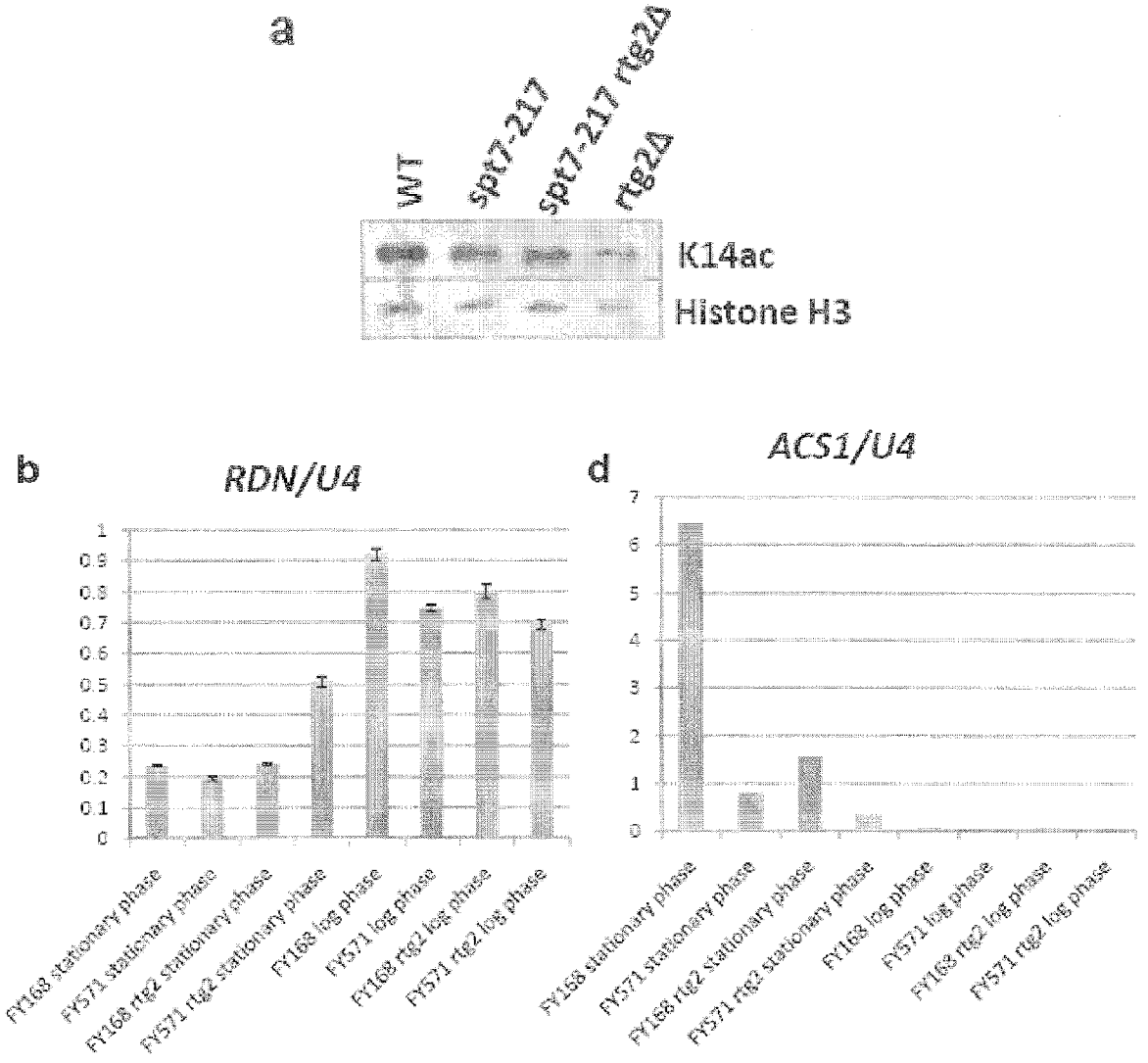

a
WT
spt7-217
spt7-217 rtg2Δ
rtg2Δ
K14ac
Histone H3
b
RDN/U4
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
FY168 stationary phase
FY571 stationary phase
FY168 rtg2 stationary phase
FY571 rtg2 stationary phase
FY168 log phase
FY571 log phase
FY168 rtg2 log phase
FY571 rtg2 log phase
d
ACS1/U4
7
6
5
4
3
2
1
0
FY168 stationary phase
FY571 stationary phase
FY168 rtg2 stationary phase
FY571 rtg2 stationary phase
FY168 log phase
FY571 log phase
FY168 rtg2 log phase
FY571 rtg2 log phase

Figure 6 (cont)

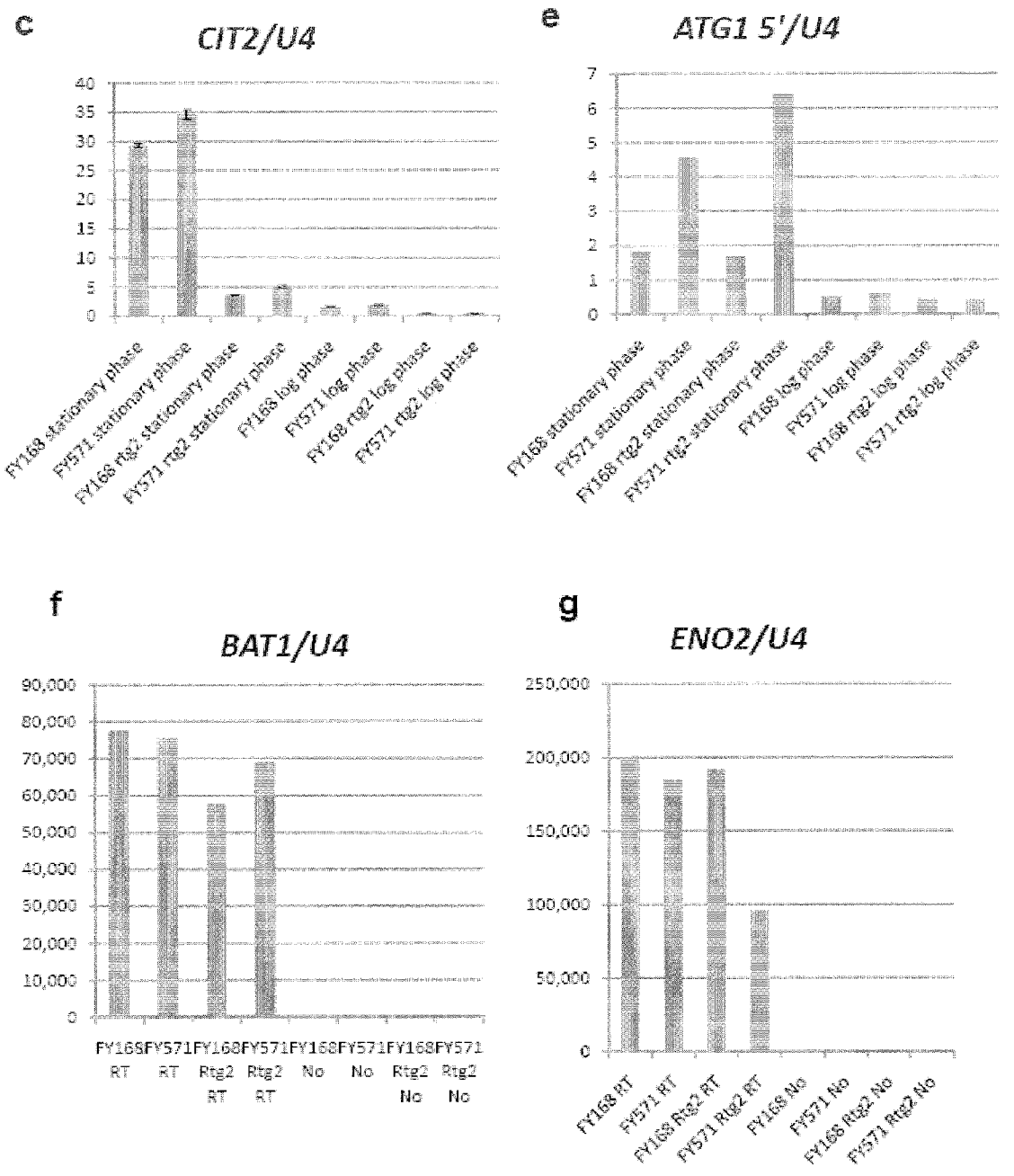


Figure 6 (cont)

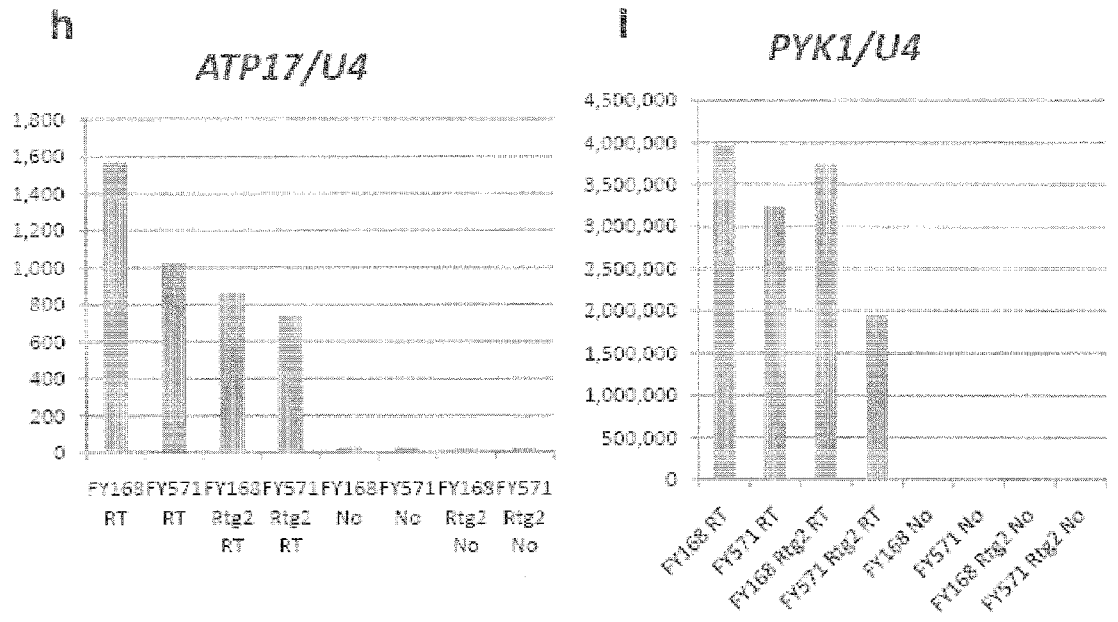


Figure 7

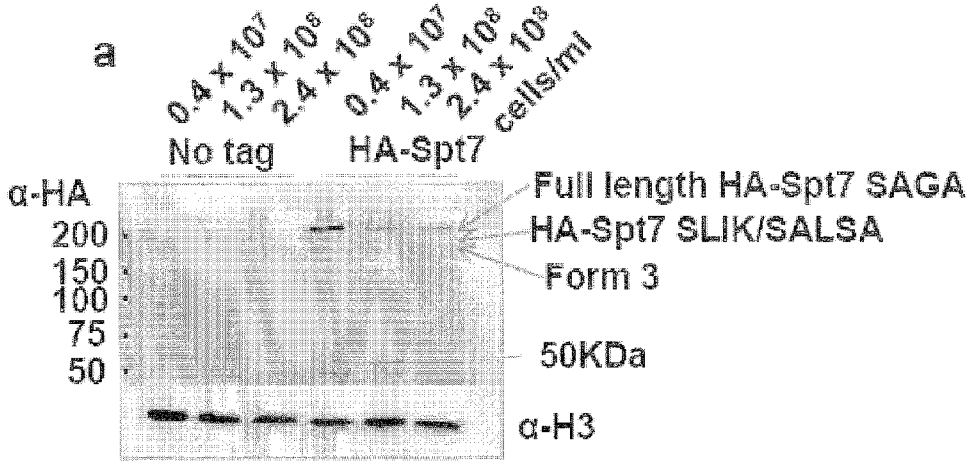


Figure 8

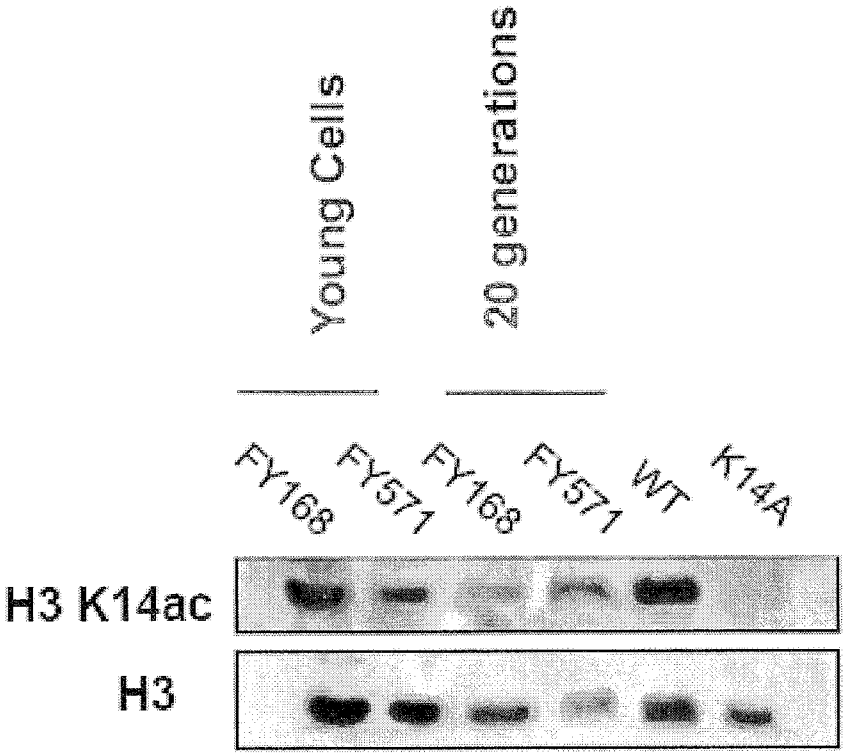
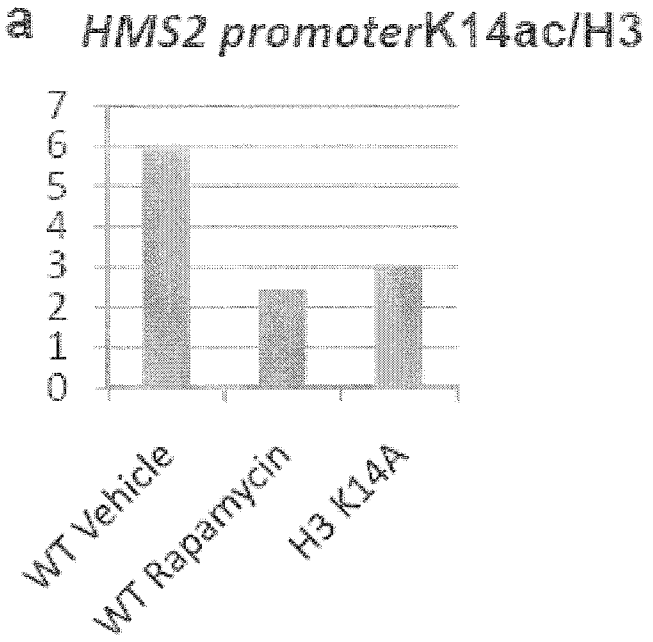

Young Cells
20 generations
FY168
FY571
FY168
FY571
WT
K14A
H3 K14ac
H3

Figure 9


a
HMS2 promoterK14ac/H3
7
6
5
4
3
2
1
0
WT Vehicle
WT Rapamycin
H3 K14A

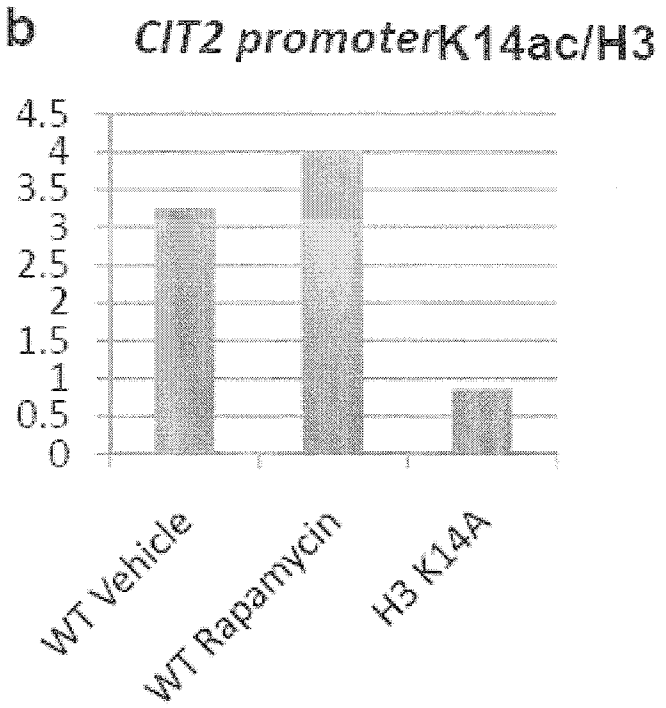

b
CIT2 promoterK14ac/H3
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
WT Vehicle
WT Rapamycin
H3 K14A

Figure 10

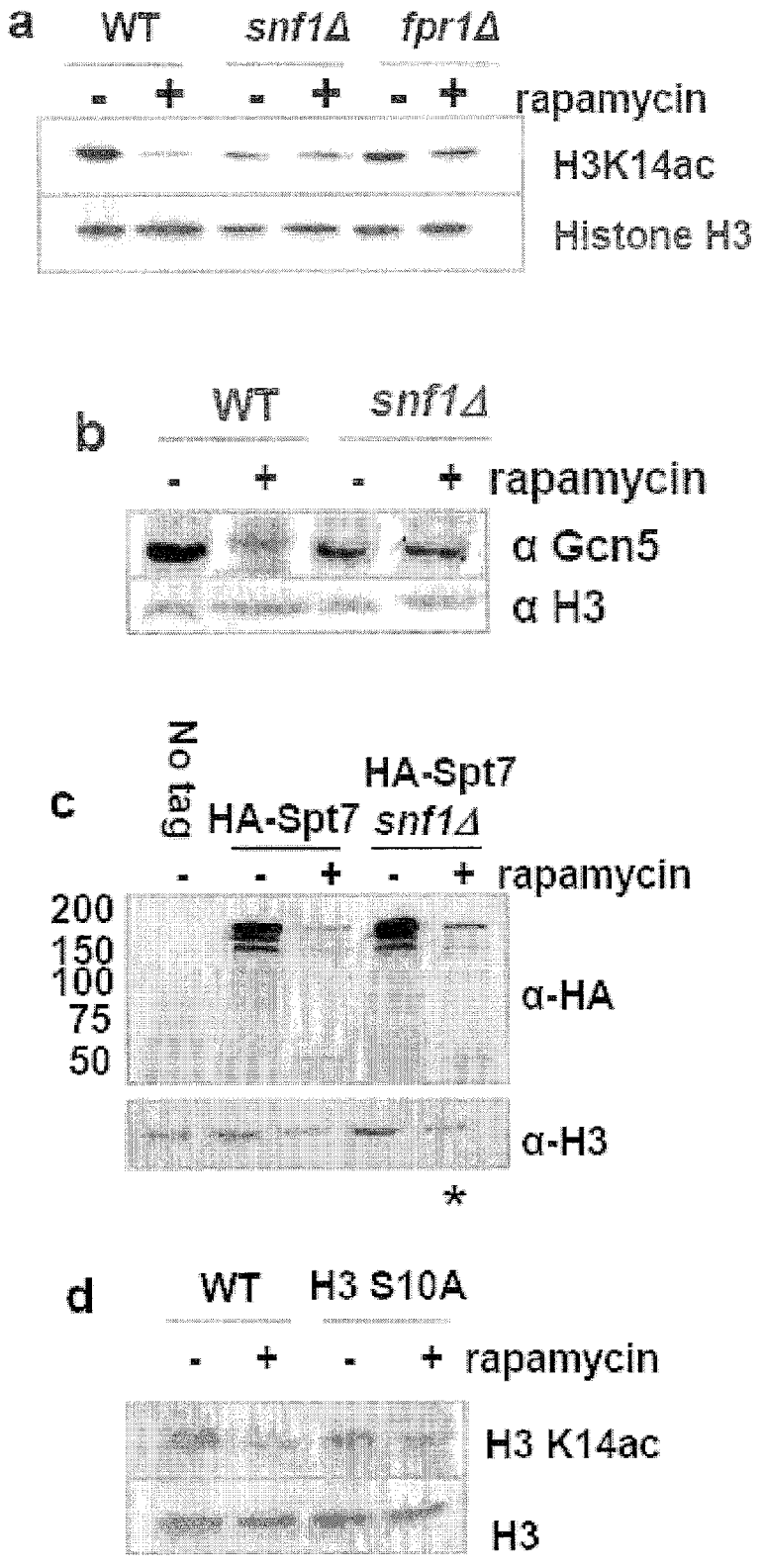

a
WT
snf1Δ
fpr1Δ
- + - + - +
rapamycin
H3K14ac
Histone H3
b
WT
snf1Δ
- + - +
rapamycin
α Gcn5
α H3
c
No tag
HA-Spt7
HA-Spt7
snf1Δ
- - + - +
rapamycin
200
150
100
75
50
α-HA
α-H3
*
d
WT
H3 S10A
- + - +
rapamycin
H3 K14ac
H3

Figure 10 (cont)

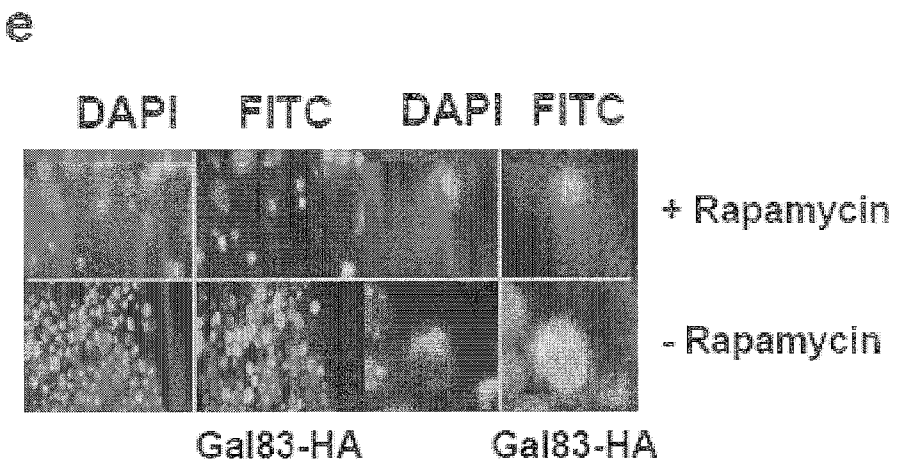


Figure 11

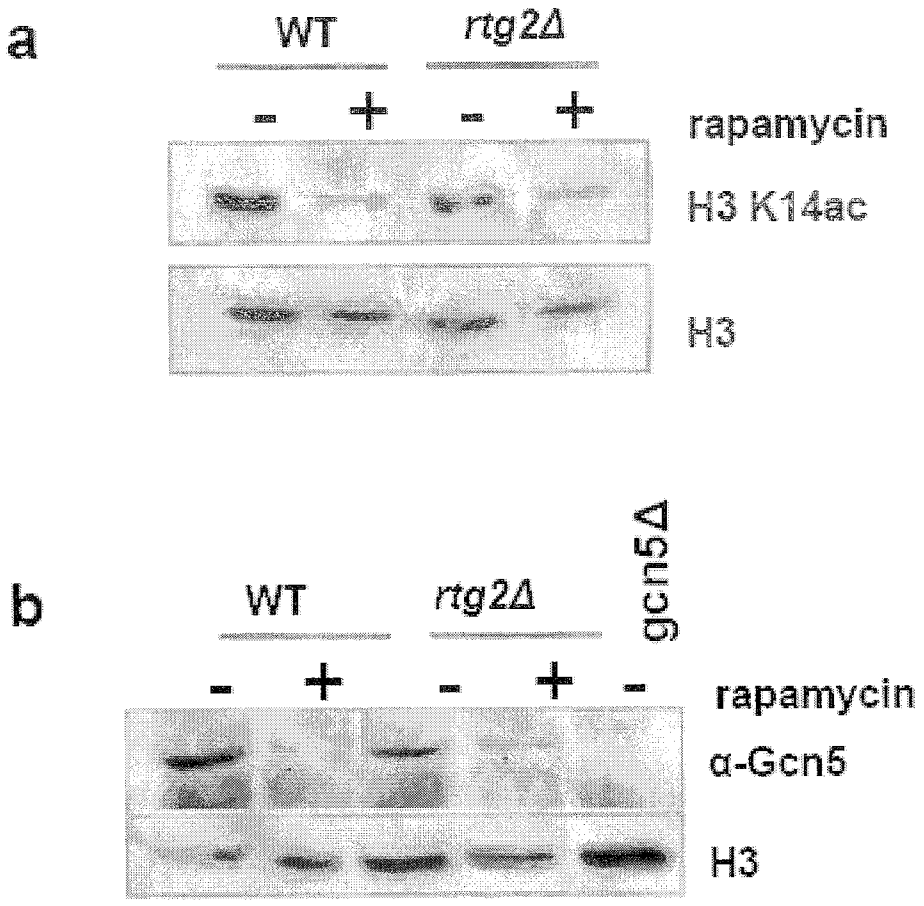

a
WT
rtg2Δ
- + - +
rapamycin
H3 K14ac
H3
b
WT
rtg2Δ
gcn5Δ
- + - + -
rapamycin
α-Gcn5
H3

Figure 12

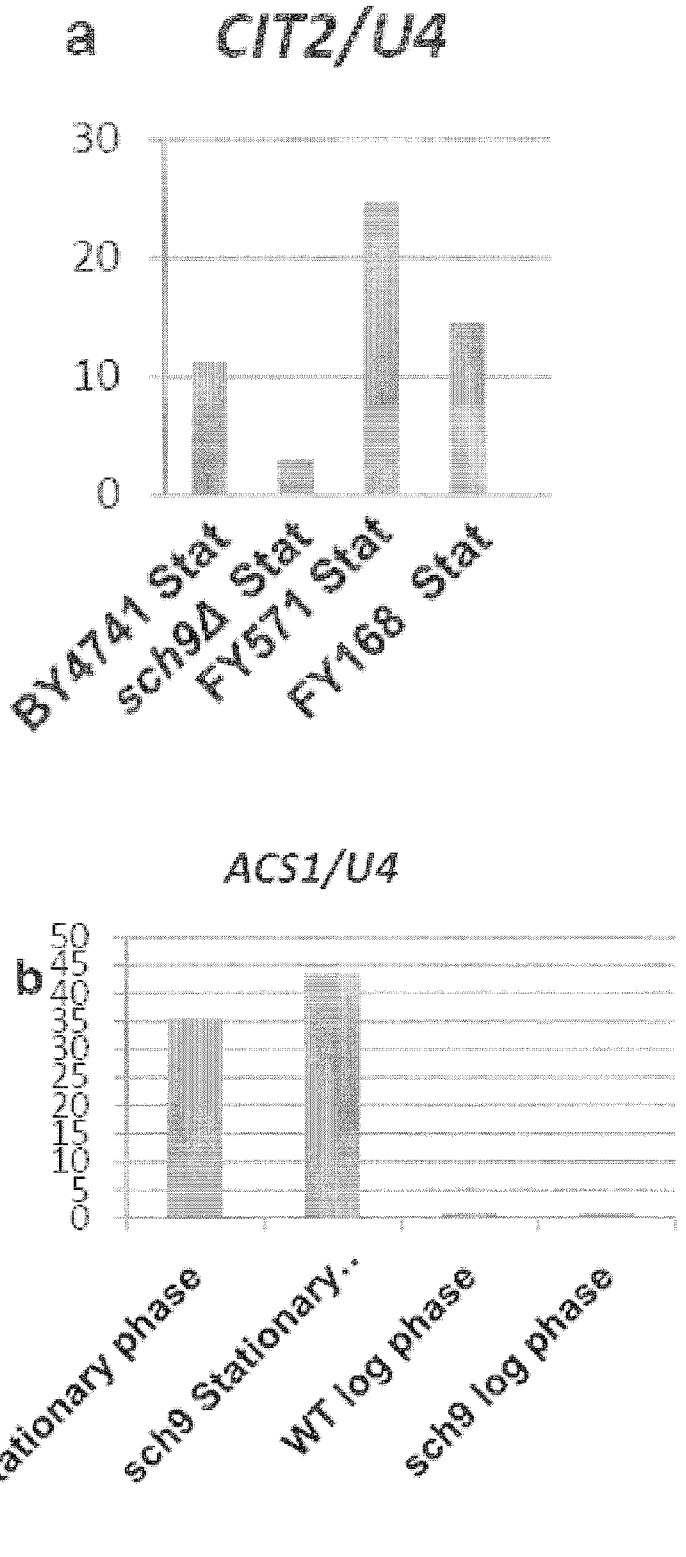

a
CIT2/U4
30
20
10
0
BY4741 Stat
sch9Δ Stat
FY571 Stat
FY168 Stat
ACS1/U4
b
50
45
40
35
30
25
20
15
10
5
0
WT stationary phase
sch9 Stationary..
WT log phase
sch9 log phase

Figure 12 (cont)

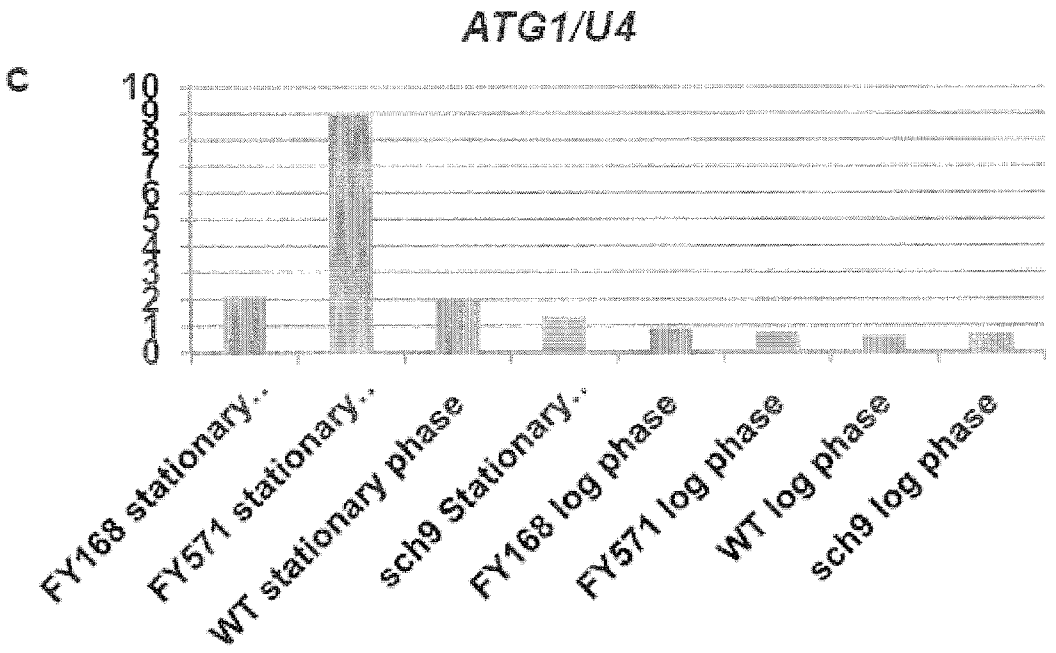


Figure 13

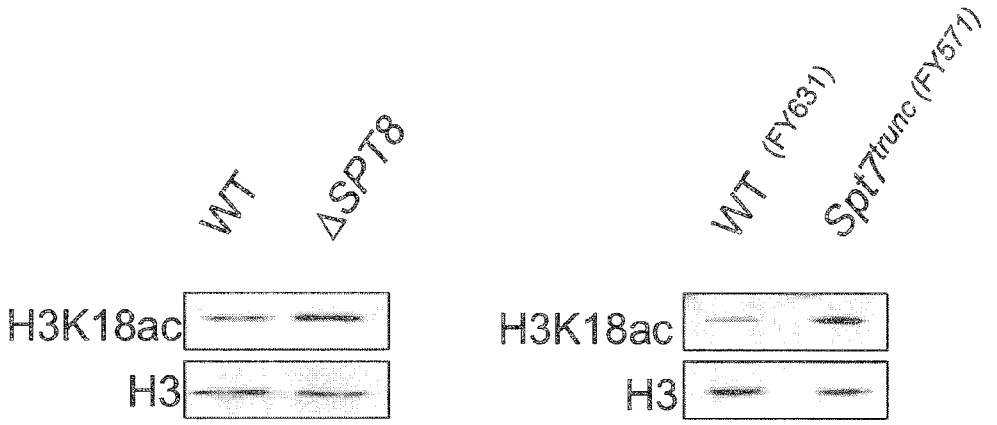


Figure 14

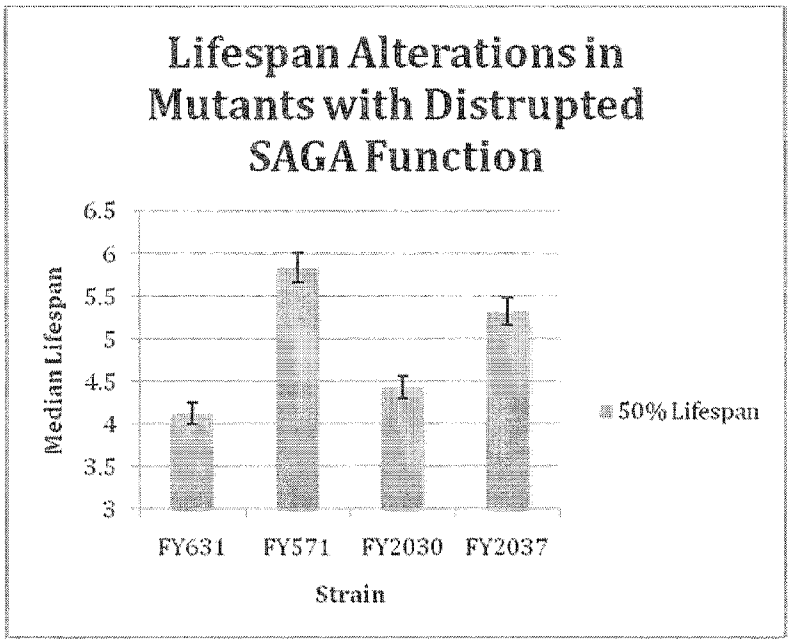
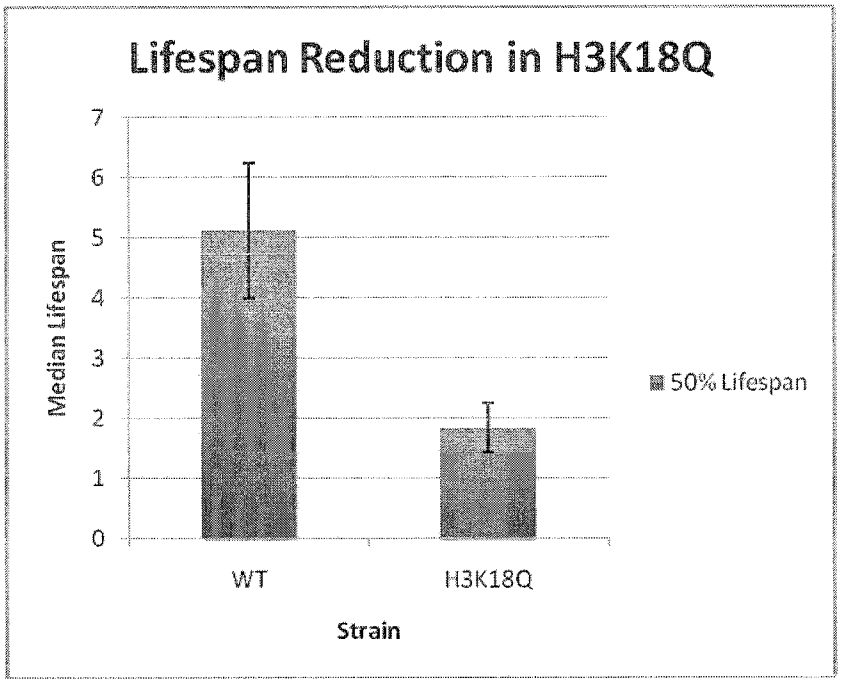


Figure 15


Lifespan Reduction in H3K18Q
Median Lifespan
7
6
5
4
3
2
1
0
WT
H3K18Q
Strain
50% Lifespan

SCREENING METHOD FOR CELL AGING

FIELD OF INVENTION

The present invention relates to methods of screening to identify compounds which have an effect on ageing of a cell, more particularly chronological ageing of a cell, methods of diagnosing disorders related to a change in the chronological life span of a cell.

BACKGROUND

The target of rapamycin complex, TORC1, is conserved from yeast to man and has critical roles in sensing and signalling the nutrient and stress status of the cell, thus controlling the balance between cell growth[1-5] and cell survival[6-11]. In budding yeast TORC1 promotes fermentative growth on glucose and down regulates respiration[12, 13]. TORC1 contains a phosphatidylinositol kinase (PI3-K)-related kinase, either Tor1 or Tor2. The macrolide rapamycin[14], in a complex with Fpr1 (Fk506-sensitive Proline Rotamase), binds to Tor1/2 causing cells to enter a state that resembles nutrient limitation[15] probably due to a change in the substrate specificity of the Tor kinase[16]. This new state of the cell is associated with changes in patterns of gene expression, particularly genes required for respiration and stress resistance[6,10,17,18]. The expression of many TORC1 genes is dependent on the SAGA family of transcriptional co-activator complexes including SAGA (Spt-Ada-Gcn5-Acetyltransferase)[19,20], SLIK (SAGA-like)[21] and SALSA (SAGA altered, Spt8 absent)[22-24]. SAGA, SLIK and SALSA contain the lysine acetyltransferase (KAT) Gcn5[21-23], with lysine 14 on histone H3 (H3K14ac) as a substrate, but differ in their abundance, the genes they regulate and subunit composition[19,24]

The inventors have discovered that H3K18 acetylation, is central to a mechanism that controls the balance between cell growth and longevity. They have also identified a number of genes involved in the SAGA SLIK and SALSA complexes whose disruption results in an increase in chronological lifespan.

SUMMARY OF THE INVENTION

According to a first aspect of the present invention there is provided a method for increasing the chronological lifespan of a cell comprising disrupting the function of at least one of the SAGA, SLIK and/or SALSA complexes in said cell.

According to a second aspect of the present invention there is provided a method for identifying a potential modulator of the chronological life span (CLS) of a cell, comprising the steps of

i) contacting a cell having a known Histone 3 Lysine 18 (H3K18) acetylation status with a test compound; and

ii) determining if said compound has an effect on the acetylation status of H3K18 in said cell;

wherein, a change in the acetylation status of H3K18 in the cell indicates that the compound modulates CLS.

According to a third aspect of the present invention there is provided a modulator of the CLS of a cell identified by the method of the second aspect.

According to an fourth aspect of the present invention there is provided a method for identifying the replication status of a cell comprising identifying the acetylation state of H3K18, wherein the presence of an acetyl modification of H3K18 indicates that the cell is an actively replicating cell and the absence of an acetyl modification of H3K18 indicates a cell which is no longer replicating.

According to a fifth aspect of the present invention there is provided a method of identifying a change in the CLS of a cell comprising identifying the acetylation state of H3K18 in the cell and comparing this to the acetylation state of a control cell, wherein loss of H3K18Ac when compared to the control cell indicates an increased CLS and acquisition of H3K18Ac when compared to the control cell indicates a reduced CLS.

According to a sixth aspect of the present invention there is provided a method of diagnosing a disorder associated with a change in the CLS of a cell, said method comprising identifying the acetylation status of H3K18 in a cell previously isolated from a subject and comparing said acetylation status to the acetylation status of a control cell.

DETAILED DESCRIPTION OF THE INVENTION

It will be understood that any preferred embodiments described herein in relation to one aspect of the present invention can, where appropriate, be equally applicable to any other aspect of the invention.

According to a first aspect there is provided a meth. for increasing the chronological lifespan of a cell comprising disrupting the function of at least one of the SAGA, SLIK and/or SALSA complexes in said cell.

As used herein the term chronological life span refers to the time cells in a stationary phase culture remain viable.

It will be understood that the function of the at least one of the SAGA, SLIK and/or SALSA complexes may be disrupted directly or indirectly. These complexes play a crucial role in controlling of the acetylation state and CLS of a cell, but differ in their levels depending upon the status of the cell and its environment.

As used herein the terms directly and indirectly in relation to interaction with the recited complexes refer to an interaction with either the complex itself, or with a gene product from a gene encoding a peptide which forms part of the complex, or with the gene product from a gene which allows the complex to form.

Preferably, disruption is effected through disruption of at least one gene or a product of at least one gene selected from the group consisting of Spt3, Rtg2, Gcn5, Ubp8, Spt7, Spt8 and/or Snf1 or their homologues.

The term homologue as used herein refers to an analogous gene from a different organism which performs the same function and in general shows some degree of sequence homology. The skilled person will understand that the above genes from *S. cerevisiae* have homologues in other organisms including mammels. For example, Spt3 shows homology to human SUPT3H-203; Gcn5 shows homology to human KAT2B-001 and KAT2A-001; Spt7 shows homology to human SUPT7H and SNF1 shows homology to PRKAA1 and PRKAA2.

It will be understood that these genes encode products which form part of the SAGA, SLIK and/or SALSA complexes, or interact with said complexes in manner so as to affect acetylation of histones in a cell.

Preferably, the disruption is effected through disruption of SPT7 (SEQ ID NO:11) or SPT7-217 (SEQ ID NO:19).

As used herein the term "disrupting the function", "disruption of the function" or "disrupts the function" when used in relation to a gene or gene product refers to disrupting the expression of the gene or disrupting the activity of the encoded polypeptide. It will be further understood that any stage of gene expression between initiation of transcription and production of a mature protein can be disrupted. The skilled person will understand that this will include epigenetic means of controlling gene expression through control-

ling chromatin structure as well as transcriptional, translational and post translation means of controlling gene expression.

It will be understood that by disrupting expression of a gene as used herein is meant preventing or inhibiting production of a functional polypeptide by any means known in the art and that disrupting the activity of the encoded polypeptide refers to disrupting interaction of the functional polypeptide with one or more of it's binding partners such that the polypeptide does not perform it's function. The production or function may be fully or partially prevented. In one embodiment, preferably the production or function of the gene product is fully prevented, i.e. there is no active gene product. In some instances the production or function of the gene product may be disrupted such that there is only about 5%, about 10% about 20%, about 30%, about 50%, about 60%, about 70%, about 80%, about 90% or about 95% of the wild type level of expression remaining.

As used herein by inhibiting production of a functional polypeptide it is meant that the production of the gene product may be prevented or inhibited by (a) knocking out said gene; (b) post-transcriptionally silencing said gene through for example the use of iRNA or antisense RNA (gene silencing); (c) transcriptionally silencing said gene by, for example, epigenetic techniques; (d) preventing or altering the function of the gene product by the introduction of at least one point mutation; (e) post translationally inactivating the gene product.

In one preferred embodiment, expression of the gene or homologue is disrupted by iRNA.

Preferably, the cell is transformed with a plasmid/vector encoding an iRNA under control of a promoter. It will be apparent that this promoter may be a constitutive promoter and/or a tissue specific promoter.

As used herein the term iRNA refers to RNA interference (RNAi). This is a method of post-transcriptional gene silencing (PIGS) in eukaryotes induced by the direct introduction of dsRNA (Fire A, et al., (1998)).

In a further preferred embodiment expression of the gene is disrupted at the transcriptional/DNA level. Preferably, said disruption is effected by insertion of at least one nucleotide into the gene or deletion of at least one nucleotide from the gene.

In a further embodiment, the disruption of the gene is effected by introduction of at least one point mutation.

It will be understood that in the case of disruption of the interaction of the polypeptide with one or more of it's binding partners. this disruption can be by any suitable means, for example, competitive inhibition, non-competitive inhibition, mixed inhibition or uncompetitive inhibition.

The present invention encompasses the use of sequences having a degree of sequence identity or sequence homology with amino acid sequences of the polypeptides defined herein or of any nucleotide sequence encoding such a polypeptide (hereinafter referred to as a "homologous sequence(s)"). Here, the term "homologous" means an entity having a certain homology with the subject amino acid sequences and the subject nucleotide sequences. Here, the term "homology" can be equated with "identity".

The homologous amino acid sequence and/or nucleotide sequence should provide and/or encode a polypeptide which retains the functional activity and/or enhances the activity of the enzyme.

In the present context, a homologous sequence is taken to include an amino acid sequence which may be at least 50, 60, 70, 75, 80, 85 or 90% identical, preferably at least 95%, 97%, 98% or 99% identical to the subject sequence. Typically, the homologues will comprise the same active sites etc. as the subject amino acid sequence. Although homology can also be considered in terms of similarity (i.e. amino acid residues having similar chemical properties/functions).

In the present context, a homologous sequence is taken to include nucleotide sequence which may be at least 50, 60, 70, 75, 80, 85 or 90% identical, preferably at least 95%, 97%, 98% or 99% identical to a nucleotide sequence encoding a polypeptide of the present invention (the subject sequence). Typically, the homologues will comprise the same sequences that code for the active sites etc. as the subject sequence. Although homology can also be considered in terms of similarity (i.e. amino acid residues having similar chemical properties/functions).

Homology comparisons can be conducted by eye, or more usually, with the aid of readily available sequence comparison programs. These commercially available computer programs can calculate % homology between two or more sequences.

% homology may be calculated over contiguous sequences, i.e. one sequence is aligned with the other sequence and each amino acid in one sequence is directly compared with the corresponding amino acid in the other sequence, one residue at a time. This is called an "ungapped" alignment. Typically, such ungapped alignments are performed only over a relatively short number of residues.

Although this is a very simple and consistent method, it fails to take into consideration that, for example, in an otherwise identical pair of sequences, one insertion or deletion will cause the following amino acid residues to be put out of alignment, thus potentially resulting in a large reduction in % homology when a global alignment is performed.

Calculation of maximum % homology therefore firstly requires the production of an optimal alignment, taking into consideration gap penalties. A suitable computer program for carrying out such an alignment is the Vector NTI (Invitrogen Corp.). Examples of software that can perform sequence comparisons include, but are not limited to, the BLAST package (see Ausubel et al 1999 Short Protocols in Molecular Biology, 4th Ed—Chapter 18), BLAST 2 (see FEMS Microbiol Lett 1999 174(2): 247-50; FEMS Microbiol Lett 1999 177(1): 187-8 and tatian@ncbi.nlm.nih.qov), FASTA (Altschul et al 1990 J. Mol. Biol. 403-410) and AlignX for example. At least BLAST, BLAST 2 and FASTA are available for offline and online searching (see Ausubel et al 1999, pages 7-58 to 7-60).

Suitably, the degree of identity with regard to a nucleotide sequence is determined over at least 20 contiguous nucleotides, preferably over at least 30 contiguous nucleotides, preferably over at least 40 contiguous nucleotides, preferably over at least 50 contiguous nucleotides, preferably over at least 60 contiguous nucleotides, preferably over at least 100 contiguous nucleotides.

Suitably, the degree of identity with regard to a nucleotide sequence may be determined over the whole sequence.

As used herein, the term fragment refers to a fragment of the sequence which provides and/or encodes a polypeptide which retains the functional activity and/or enhances the activity of the enzyme.

When referring to a polypeptide fragment, preferably, the fragment is at least 50 amino acids in length. More preferably, the fragment comprises at least 100, 200, 300, 400 or 500 600, 700, 800, 900 or 1000 continuous amino acids from the subject sequence, for example SEQ ID NO:19, up to and including a polypeptide comprising one amino acid less than the full length protein.

When referring to a polynucleotide fragment, preferably the fragment comprises at least 100 nucleotides, more pref-

erably, at least 200, 500, 800, 1000, 1500 or more nucleotides, up to and including a polynucleotide comprising one nucleotide less than the full length polynucleotide.

It will be understood by the skilled person that polynucleotides encoding a particular polypeptide can differ from each other due to the degeneracy of the genetic code. Included herein are the use of such polynucleotides encoding the polypeptide of the present invention.

It will be further apparent to the skilled person that the term homologous sequence in relation to a polynucleotide sequence can refer to a sequence which binds under stringent conditions to the polynucleotide sequence.

Hybridisation conditions are based on the melting temperature (Tm) of the nucleotide binding complex, as taught in Berger and Kimmel (1987, Guide to Molecular Cloning Techniques, Methods in Enzymology, Vol. 152, Academic Press, San Diego Calif.), and confer a defined "stringency" as explained below.

Maximum stringency typically occurs at about Tm-5° C. (5° C. below the Tm of the probe); high stringency at about 5° C. to 10° C. below Tm; intermediate stringency at about 10° C. to 20° C. below Tm; and low stringency at about 20° C. t. 25° C. below Tm. As will be understood by those of skill in the art, a maximum stringency hybridisation can be used to identify or detect identical nucleotide sequences while an intermediate (or low) stringency hybridisation can be used to identify or detect similar or related polynucleotide sequences.

In a preferred aspect, the present invention covers nucleotide sequences that can hybridise to the nucleotide sequence of the present invention under stringent conditions (e.g. 65° C. and 0.1×SSC {1×SSC=0.15 M NaCl, 0.015 M Na_3 Citrate pH 7.0). Where the nucleotide sequence of the invention is double-stranded, both strands of the duplex, either individually or in combination, are encompassed by the present invention. Where the nucleotide sequence is single-stranded, it is to be understood that the complementary sequence of that nucleotide sequence is also included within the scope of the present invention.

Nucleotide sequences which are not 100% homologous to the sequences of the present invention but fall within the scope of the invention can be obtained in a number of ways. Other variants of the sequences described herein may be obtained for example by probing DNA libraries made from a range of sources. In addition, other viral/bacterial, or cellular homologues particularly cellular homologues found in mammalian cells (e.g. rat, mouse, bovine and primate cells), may be obtained and such homologues and fragments thereof in general will be capable of selectively hybridising to the sequences shown in the sequence listing herein. Such sequences may be obtained by probing cDNA libraries made from or genomic DNA libraries from other animal species, and probing such libraries with probes comprising all or part of the nucleotide sequence set out in herein under conditions of medium to high stringency. Similar considerations apply to obtaining species homologues and allelic variants of the amino acid and/or nucleotide sequences of the present invention. In another aspect of the present invention there is provided a method for identifying a potential modulator of the chronological life span (CLS) of a cell, comprising the steps of

i) contacting a cell having a known Histone 3 Lysine 18 (H3K18) acetylation status with a test compound; and

ii) determining if said compound has an effect the acetylation status of H3K18 in said cell;

wherein, a change in the acetylation status of H3K18 in the cell indicates that the compound modulates CLS.

It is known that modification of the histone components of chromatin often reflect whether genes are active or repressed and these changes are globally regulated by enzymes that deposit or remove specific modifications. On active genes, the chromatin is often modified by lysine (K) acetylation (ac) or methylation (me), particularly of histone H3. The inventors have identified a new lysine in histone H3 whose modification status appears to play a critical role in determining the lifespan of a cell.

As used herein, the term modulator of the chronological life span refers to a compound which has an effect on the CLS of the cell. This effect may be to increase the CLS of the cell or to decrease the CLS of the cell. It will be understood that, dependent upon the purpose to which the compound is to be put, either effect may be desirable.

It will be understood that the compound referred to herein may be any suitable compound and may be, for example, a small molecule compound or equally a biological molecule such as a peptide or nucleic acid.

Preferably, the compound interacts with at least one gene or a product of at least one gene selected from the group consisting of Spt3 (SEQ ID NO: 22), Rtg2 (SEQ ID NO: 4), Gcn5 (SEQ ID NO: 6), Ubp8 (SEQ ID NO: 10), Spt7 (SEQ ID NO: 12), Spt8 (SEQ ID NO: 14) and/or Snf1 (SEQ ID NO: 16) or their homologues.

It will be apparent to the skilled person that the gene with which the compound interacts can be identified through the use of various knock out mutant strains.

Methods of producing such strains are well known to the skilled person and include for example, insertion of one or more nucleotides into the coding region of the gene. It will be understood that, as used herein, the term product of at least one gene refers to either a nucleic acid, e.g. mRNA, or peptide product.

In a further preferred embodiment, the compound interacts with the gene designated Acs1 (SEQ ID No: 18) or a product of the gene designated Acs1.

It will be further apparent to the skilled person that the acetylation status of H3K18 can be identified by any suitable means known in the art.

In one embodiment, the acetylation status is determined by measurement of mitochondrial respiration.

It will be understood by the skilled person that any suitable method for measuring mitochondrial respiration can be used. For example, mitochondrial respiration can be measured by incubating the cells in the presence DIOC6 and visualising the cells.

In an alternative embodiment, the acetylation status is determined by indirect immunofluorescence with monoclonal antibodies against H3K18ac on live or fixed cells.

The present invention also provides methods for identifying the replication status of a cell or identifying a change in the CLS of a cell.

As used herein, the term identifying the replication status refers to identifying whether a particular cell or population of cells is actively dividing, or capable of actively dividing or whether the cell or population of cells are no longer able divide.

As used herein, the term identifying a change in the CLS of a cell refers to identifying a step change in a cell or population of cells from a state in which it/they is/are capable of actively dividing to a state in which it/they can no longer divide or vice versa.

It will be understood that this change can be deliberately induced or can occur naturally or through exposure to environmental factors.

Preferably, the cell is a mammalian cell. More preferably, the cell is a human cell. In one preferred embodiment, the cell is an induced pluripotent stem cell.

The skilled person will understand that an induced pluripotent stem cell is typically a somatic cell which has been caused to regress to a pluripotent state either by exposure to certain chemicals or through transfection with, for example, various viruses.

In a further preferred embodiment the cell is a cell suspected of being neoplastic and/or cancerous. Preferably, the cell is a cell from a sample which has previously been isolated from a patient suspected of having or at risk of developing cancer.

In a further aspect, their is provided a method of diagnosing a disorder associated with a change in the CLS of a cell, said method comprising identifying the acetylation status of H3K18 of a cell previously isolated from a subject and comparing said acetylation status to the acetylation status of a control cell.

As used herein, the term control cell refers to a cell of the same tissue type as that isolated from the subject, the control cell being isolated from healthy tissue and having a known acetylation status.

Preferably, said disorder is selected from the group comprising an age related disorder, cancer, a blood disorder, Parkinson's disease or Alzheimer's disease.

The invention will be further described with reference to the figures. References to strains in the figures refer to the strains disclosed in Table 1. In the figures:—

FIG. **1** H3K14ac by SAGA reflects growth. FIG. **1** shows Western blots showing levels of various post-translational modifications to histone H3, in various backgrounds including HA-Spt7 and Gcn5 in total cell extract prepared from cells mock-treated or treated with 10 μM rapamycin for up to 180 minutes in the BY4741 background (a, b, c, d), FY168 and FY571 (e, h), FY2 and FY2030 (f) and JR-52A (g). In panel e The version of Spt7 expressed from the spt7-217 allele in FY571 is truncated at amino acid 1119 and has lost 213 C-terminal residues.

FIG. **2** SAGA and K14ac influence ageing. Western blots showing levels of K14ac (a) and HA-Spt7 (b) in total protein prepared from 1×10^8 cells of the FY2030 background (a, b) or FY168 and FY571 (c), subject to biotinylation, growth for 10 or 20 generations in exponential culture (YPD) and isolation using magnetic streptavidin beads. Young cells (majority less than 5 generations old) were prepared from the remaining non-biotinylated cells. * indicates a processed version of histone H3.

FIG. **3** Control of SAGA, SLIK and K14ac.Western blots showing levels of H3K14ac Gcn5 or HA-Spt7 in total cell extracts prepared from the strains indicated (genotype shown in Table 1) after growth in the presence of 10 μM rapamycin (+) or mock-treated (−) for 3 hours. WT strains are BY4741.

FIG. **4** Rtg2 and SLIK determine chronological lifespan. a FY168 (WT), FY571 (Spt7-217) and rtg2Δ derivatives in exponential phase stained with DiOC6 to assess mitochondrial membrane potential (ψ). Scale bar is 10 μm. b Serial ten-fold dilutions of cells from strains indicated grown with aeration to stationary phase in CSM containing 3% glucose and plated onto YDP on the day shown to assess viability. The average lifespan (time in days to 50% drop in viability) was calculated from colony counts. c Fluorographs of total protein extracts in exponential phase treated without or with cyclohexamide to inhibit cytoplasmic translation and pulse labelled for 15 minutes with 35S methionine.

FIG. **5** shows Western blots showing levels of various post-translational modifications to histone H3 in total cell extract prepared from BY4741 in exponential or early stationary phase.

FIG. **6** a shows the effect of expressing a C-terminally truncated version of Spt7 (Spt7-217) in strain FY571 and derivatives on K14ac and gene expression. FIGS. **6***b-i* show the effect of growth phase and the presence of RTG2 on the induction of various genes.

FIG. **7** shows HA-Spt7 undergoes C-terminal processing in cells entering stationary phase.

FIG. **8** shows K14ac is reduced as cells age.

FIG. **9** shows the effect of Rapamycin on K14ac at CIT2 (SLIK induced) or HMS2 (not induced) by ChIP normalised to histone H3. ChIP monitored by real time PCR[53], expressed as a percentage of input and normalised to levels of histone H3 in three preparations of chromatin, at the 5' region of the genes shown.

FIG. **10** shows that Snf1 is required for the rapamycin dependent reduction in K14ac on rapamycin treatment. a-d Western blots showing levels of modifications at H3 on total cell extracts prepared from the strains indicated in the LPY8056 background (d), BY4741 (a-b, f-g) or FY3 (c). n=3 for all experiments shown. e Indirect immunofluorescence with FITC tagged anti-HA antibody (right panel) or DAPI (DNA) (left panel) of Gal83-HA. Cells were treated +/−10 μM rapamycin for up to 3 hours.

FIG. **11** shows Rtg2 is required for optimal levels of K14ac but K14ac is rapamycin sensitive in a rtg2Δ strain. Western blots showing levels of modifications at H3 (a) and Gcn5 (b) in total cell extracts prepared from the strains indicated in the BY4741 background. Cells were treated +/−10 μM rapamycin for up to 3 hours. Rtg2 is negatively regulated by the Lst8 component of TORC1[66] and this repression is relieved by loss of TORC1 signalling or rapamycin treatment. Rtg2 is a component of SLIK[11] required for the induction of the retrograde responsive genes in quiescent cells.

FIG. **12** shows the effect of loss of Sch9 on the inducibility of CIT2, ATG1 and ACS1 in stationary phase. This figure shows reverse transcription real time PCR quantitation of RNA for the genes shown. The results suggest that Sch9 is required to maintain the integrity of SALSA and SLIK in stationary phase cultures. Consistent with this we show that the induction of ACS1 is independent of Sch9 (data in FIG. **9** suggests that this gene is dependent on Rtg2 dependent nuclear uptake of Rtg1/3 but not on SLIK). By contrast, CIT2 (SLIK/Rtg2—dependent) and ATG1 (SALSA but not SLIK dependent) require Sch9 for their expression.

FIG. **13** is a western blot showing that disruption of the SAGA complex results in an increase H3K18 acetylation.

FIG. **14** is a graph showing that disruption of SAGA extends the chronological lifespan of yeast cells.

FIG. **15** is a graph showing that disruption of H3K18 acetylation results in a significant reduction in chronological lifespan of yeast cells.

Materials and Methods

Details of strains are provided in the Table 1. Yeast were grown at 30° C. in rich medium (YPD), 1% bactpopeptone, 1% Difco yeast extract (BD and Co.), 2% glucose to a density of 0.4×10^6 cells/ml and treated with 10 μM rapamycin in 90% ethanol/10% Tween20 or mock treated for up to three hours. Details for preparation of whole cell extracts, western blotting and antibodies used, preparation of RNA and RNA quantitation, chromatin immunoprecipitation (ChiP), protocols for ageing, assessment of ERCs and chronological ageing assays are set out below.

TABLE 1

Strain	Parent	Genotype	Origin
RMY200 WT		MATa; ade2-10; 1 his3Δ200; lys2-801; trp1Δ901; ura3-52; hht1, hhf1::LEU2; hht2, hhf2::HIS3 plus pRM200 (CEN TRP1 HHF2 HHT2)	Michael Grunstein
H3 K14R	RMY200	Plus pRM200 (hht2 K14R)	Michael Grunstein
H3 K18R	RMY200	plus pRM200 (hht2 K18R)	Michael Grunstein
YSL151 WT		ura3-5; his3Δ20; leu2Δ; trp1Δ63 lys2-128Δ(hht1-hhf1)::LEU2; (hht2-hhf2)::HIS3; pTRP1-HHT2-HHF2	Shelley Berger
H3 K4A	YSL151	Plus pTRP1 (hht2 K4A)	Shelley Berger
YZS276		MATa; hta1-htb1Δ::LEU2 hta2-htb2Δ leu2-3,-112 his3-11,-15 trp1-1 ura3-1 ade2-1 can1-100 (pZS145 HTA1-Flag-HTB1 CEN HIS3)	David Allis
H2B K123R	YZS276	Plus pZS14 (htb1 K123R)	David Allis
LPY8056		MATa; his3Δ200; leu2Δ1; ura3-52; trp1Δ63; lys2-128δ; (hht1-hhf1)Δ::LEU2 plus pRS314B (HHF2 HHT2)	Shelley Berger
H3 S10A	LPY8056	Plus PRS314B (hhf2 S10A)	Shelley Berger
H3 K14A	LPY8056	Plus PRS314B (hhf2 K14A)	Shelley Berger
H3 S10A K14A	LPY8056	Plus PRS314B (hhf2 S10A K14A)	Shelley Berger
BY4741		MATa; his3Δ; leu2Δ; met15Δ; ura3	Euroscarf
gcn5Δ	BY4741	gcn5::KanMX	Euroscarf
spp1Δ	BY4741	spp1::KanMX	Euroscarf
S288c		MATa; his3Δ1; leu2Δ0; met15Δ0; ura3Δ0	Open Biosystems
fpr1Δ	BY4741	fpr1::KanMX	Euroscarf
fpr2Δ	BY4741	fpr2::KanMX	Euroscarf
fpr3Δ	BY4741	fpr3::KanMX	Euroscarf
fpr4Δ	BY4741	fpr4::KanMX	Euroscarf
rim15Δ	BY4741	rim15::KanMX	Euroscarf
rtg2Δ	BY4741	rtg2::KanMX	Euroscarf
msn2Δ	BY4741	msn2::KanMX	Euroscarf
msn4Δ	BY4741	msn4::KanMX	Euroscarf
snf1Δ	BY4741	snf1::KanMX	Euroscarf
sch9Δ	BY4741	sch9::KanMX	Euroscarf
dot1Δ	By4741	dot1::KanMX	Euroscarf
L5487		MATa, ura3-52, leu2::hisG	Aaron Mitchel
sch9Δ	L5487	sch9::URA3	Paul Nutton
Gal83-HA	BY4741	GAL83-HA-His3MX6	This study
Gcn5-HA	JR-52A	Plus pRS314 (GCN5 3HA::his5+)	Shelley Berger
spt20Δ	BY4741	spt20::KanMX	Euroscarf
spt8Δ	BY4741	spt8::KanMX	Euroscarf
FY3		MATa; ura3Δ0	Fred Winston
FY2030 HA-Spt7	FY3	MATa; ura3Δ0; leu2Δ1; trp1Δ63; his4-917 δ; lys2-173R2 HA-SPT7-URA3	Fred Winston
HA-Spt7 snf1Δ	FY2030	snf1::KanMX	This study
HA-Spt7 sch9Δ	FY2030	sch9::KanMX	This study
FY168		MATa; leu2Δ1; his4-917 δ; lys2-173R2	Fred Winston
FY168 rtg2Δ		rtg2::KanMX	This study
FY571 spt7-217		MATa; ura3Δ0; leu2Δ1; trp1Δ63; his4-917 δ; lys2-173R2 spt7-217	Fred Winston
FY571 rtg2Δ	spt7-217	rtg2::KanMX	This study

Preparation of Yeast Whole Cell Extracts.

25 ml of cells were grown in YPD to an OD of ~0.4 A_{600} and harvested by centrifugation. For rapamycin treated cells, cells were grown to mid-log followed by the addition of 10 μM rapamycin (Sigma R0395-1 MG) for up to 3 hours and harvested by centrifugation. Cell pellets were resuspended in 300 μl 8 M urea and broken by vortexing for 5 mins following the addition of 200 μl acid-washed glass beads (Sigma). Lysates were boiled for 5 mins in standard laemmli loading buffer.

Western Blotting.

Protein extracts were subject to electrophoresis on polyacrylamide gels using standard Tris-glycine running buffer (40% (w/v) glycine, 0.25 M Tris-base, 10% (w/v) SDS) following heating at 90° C. for 3 min. Proteins were transferred onto a nitrocellulose membrane using semi-dry transfer (Bio-Rad). Successful transfer of protein was verified by Ponceu S staining (0.1% Ponceu S, 5% acetic acid). Membranes were then blocked in PBS containing 5% dry milk or BSA for 1 hour, followed by incubation with primary antibody: 1:3000 anti-H3 (Abcam ab1791), 1:5000 anti-H3 K9ac (Upstate 07-352), 1:3000 anti-H3 K14ac (Upstate 07-353), 1:5000 anti-H3 K18ac (Upstate 07-354), 1:10,000 anti-H3 K23ac (Upstate 07-355), 1:3000 anti-H3 K27ac (Upstate 07-360), 1:5000 anti-H3 K4me1 (Upstate 07-436), 1:2000 anti-H3 K4me2 (Upstate 07-030), 1:5000 anti-H3 K4me3 (Upstate 07-473), 1:500 anti-Gcn5 (Santa Cruz sc-9078), 1:5000 anti-Tubulin (Abcam ab6160), 1:1000 Anti-HA (Roche clone 3F10 11867423001) in 5% dry milk/PBS/0.5% Tween 20. Membranes were then washed for 6×5 min in PBS and incubated for 1 hour with horseradish peroxidase conjugated secondary antibody in 5% dry milk/PBS/0.5% Tween 20, and washed for 6×5 min in PBS/0.5% Tween 20. Bound antibody was visualised using a Pico West chemiluminescence kit (Pierce Biotechnology Ltd) according to manufacturer's instructions. Multiple exposures of each film were made to ensure signals detected were not saturated. Each experiment was repeated at least 3 times.

RNA Extraction and Northern Blotting.

Extraction of RNA was performed using hot phenol extraction. 15 μg of total RNA was separated on 1.1% formaldehyde gels and transferred to Magna nylon membranes and baked at 80° C. for 2 hours. The membranes were blocked by incubation for 2 hours at 65° C. with PerfectHyb Plus (Sigma). Membranes were typically exposed for 24 hours unless otherwise stated. Levels of total RNA loaded was monitored by the rRNA species, which are equal across samples unless indicated.

Isolation of Yeast at 10 or 20 Generations of Growth.

1×10^8 cells from a culture at OD_{600} of 0.2 were washed in PBS, biotinylated with 3 mg of sulfo-NSH-LC-biotin at room temperature for 15 minutes, washed 6 times with PBS and added to 1 liter of pre-warmed YPD containing 2.5% glucose and incubated for 10 generations. Harvested cells were washed in PBS. 400 ul of strepavidin beads were added and incubated with the cells on ice for 2 hours in PBS. A magnetic sorter was used to select beads with biotinylated cells attached for 20 minutes on ice with occasional mixing. The mixture was washed and reselected five times using PBS. The sorted cells were added to a second liter of prewarmed YPD and grown for an additional 10 generations, sorted and washed exactly as before. Protein or DNA was isolated from the yeast using urea and glass beads (see above) for analysis by Western blotting or by preparing sphaeroplasts and extracting total DNA by phenol chloroform extraction exactly as described[51]. The total DNA extract was separated on a 0.8% agarose gel. DNA was visualized by hybridization to radiolabelled probes.

Labelling Yeast with 35S Methionine.

Exponential cultures in synthetic complete medium with glucose were treated with or without cycloheximide (250 μg/ml in 10 ml of culture), and the incubation was continued for 5 min prior to the 15-min incubation with 100 μCi of

[^{35}S]methionine (PerkinElmer Life Sciences). Total protein was separated on a 10 or 15% SDS-PAGE gel. The gel was then treated with Enlightening (PerkinElmer Life Sciences), dried, and exposed to x-ray film for 40-72 h.

Microscopy.

Cells in exponential growth or after 2.5 days in culture (stationary phase) were incubated with the membrane-potential-sensitive dye 3,3'-dihexyloxacarbocyanine iodide (DiOC6) obtained from Molecular Probes at a concentration of 20 ng/ml for 30 minutes, washed in PBS and visualised using exposure of 1000 ms (exponential cells) or 250 ms (stationary phase cells) the FITC channel on an Olympus IX-81 fluorescence microscope with a 150 W xenon-mercury lamp and an Olympus 150X Plan NeoFluor oil-immersion objective. Brightfield images (DIC) were captures for each field.

Optimizing Conditions for Treating Cells with Rapamycin

Cells in exponential phase of growth were treated with 10 μM rapamycin in 90% ethanol/10% Tween 20 for up to 180 minutes and levels of H3K14ac and histone H3 examined. Alternatively, cells were treated with up to 20 μM rapamycin for 30 minutes. A standard set of conditions were determined and for all work in this paper involved treatment of exponentially growing cells (0.4×10^7 cell/ml) for 2 to 3 hours with 10 μM rapamycin.

Assay Showing the Dependency of Post-translational Modifications to histone H3 on the Integrity of Factors Known to Influence Modifications on Histone H3.

Total cell extracts were prepared from LPY8056 cells expressing histone H3 with alanine (A) substitutions at S10 or K14 or both residues, BY4741 carrying deletions of SPP1, encoding a factor required specifically for H3K4me3[52] or DOT1, the methyltransferase for H3K79[53,54], or YZS276 carrying a substitution at H2BK123[55], required for H3K4me2 and H3K4me3. The modifications of lysines on histone H3 were monitored by Western blotting of total cell protein extracts using antibodies specific for each modification.

HA-Spt7 Undergoes C-terminal Processing in Cells Entering Stationary Phase or Treated with Rapamycin.

Strain FY2030, expressing an N-terminally tagged version of Spt7 from the SPT7 locus and FY3, an untagged control were used for these experiments (n=9 for a). a Cells were grown in YDP to mid-log phase, post-diauxic phase or early stationary phase and total protein extracts prepared, subject to western blot using the 3F10 monoclonal antibody to reveal the HA epitope. Positions of the molecular weight markers are shown and a blot developed to reveal histone H3 levels to act as a loading control. Three high molecular weight form of HA-Spt are present, consistent with full length Spt7 in SAGA, a C-terminally truncated form missing approx 200aa found in SLIK and form 3 who function is not known[27,25]. In addition a form that migrates at 50 kDa is also evident in these and other preparations when levels of full length Spt7 drop. b A repeat of the experiment shown above showing more extensive C-terminally truncated version of Spt7 in all three growth conditions. About three of nine experiments show a profile such as this while six show more discrete bands as in a.

Indirect Immunofluoresence

The acetylation/methylation staus of a cell was assessed using indirect immunoflurescence according to the following protocol. 10-50 ml of a fresh mid-log culture of cells per sample was used. Make fresh 30% formaldehyde (3g p-formaldehyde in 5 ml PEM, add 4M NaOH until dissolved and make up to 10 ml with PEM) and add $1/10^{th}$ volume of 30% formaldehyde to the culture with agitation (in conical flask). 30s later add gluteraldehyde solution to a final concentration of 0.2% (w/v). Shake at incubation temp for 90 min. Spin cells 2K 5 min then wash 3× in PBS or PEM (100 mM Pipes pH 6.9; 1 mM EGTA, 1 mM Mg2SO4). Resuspend cells in 10 ml of PEMS (PEM in 1M Sorbitol) and add 500 μl of ICN Yeast Lytic Enzyme (10 μg/ml). Incubate at 37° C. until ~80% of cells are digested (about 15 min). Wash 3× in 10 ml of PEMS. Resuspend in 10 ml of 1% Triton X100 in PEM for 30s. Wash 3× in 10 ml PEM. Roughly assess the volume of the final pellet. Resuspend in 2 ml of PEMBAL (PEM, 0.1M L-lysine, 1% BSA (globulin free), 0.1% Na Azide) and transfer a volume which will give a 20-30 μl pellet upon a subsequent spin to each of 2 Eppendorf tubes. Put on a rotating wheel for 30 min at room temp. Spin for 10 sec. Resuspend in 50 μl of primary antibody in PEMBAL (test suitable dilution) and incubate for 16 hours on rotating wheel. Wash 3× in 1 ml PEMBAL. Resuspend in 1 ml of PEMBAL and rotate on a wheel for 30 min. Resuspend in 50 μl of Goat anti-mouse Texas Red at 20 mg/ml in PEMBAL. Incubate 16 hours on rotating wheel. Wash 3× in PEMBAL. Resuspend pellet in 100 μl PEMBAL and mount on poly L-Lysine coated coverslips. Dry with hairdryer and invert on 1 μg/ml DAPI in 100% glycerol if required. Alternatively use a FITC secondary antibody at 1/200 and incubate for 1 hour at room temperature on a wheel. N.B. cover tubes with foil during incubations with secondary antibody. The cells were then visualised

EXAMPLES

H3K14ac by SAGA Reflects Growth

The type of post-translational modification on the histone components of chromatin often reflects whether genes are active or repressed and these changes are globally regulated by enzymes that deposit or remove specific modifications. On active genes, the chromatin is often modified by lysine (K) acetylation (ac) or methylation (me), particularly on histone H3[27]. in order to identify post-translational modifications on histone H3 that reflect cell growth, we prepared total protein extracts from yeast in exponential or early stationary phase. Large and reproducible differences in the signals on Western blots allow us to correlate changes in acetylation and methylation with cell physiology. Cells in stationary phase show reductions in K14ac, K18ac and trimethylation (me3) of K4 that are not a consequence of cell-cycle arrest (FIG. **5**). These changes are similar in exponentially growing cells treated with the macrolide rapamycin, which blocks growth and proliferation[14] (FIGS. **1***a* and **10-11**), suggesting that the presence of these modifications reflects the proliferative capacity of the cells.

Gcn5 is the major acetyltransferase for K14 and K18 (FIG. **1***b*). Furthermore, the rapamycin-sensitive K14ac detectable by Western blotting is mediated by Gcn5 in SAGA (FIG. **1***c*). Strains lacking Spt8, specific to SAGA[22] or Spt20, required for the integrity of SAGA and SLIK/SALSA[23,31,32], have low levels of K14ac that do not detectably change when treated with rapamycin. In contrast, K14ac is resistant to rapamycin in a strain lacking Ubp8, a component of SAGA with ubiquitin protease activity required for processing the C-terminal region of Spt7[23,25] (FIG. **1***b*). Western blots showing levels of modifications at H3 on total cell extracts prepared from the strains indicated all in the BY4741 background are shown in FIGS. **1***c-e*. Cells were treated +/−10 μM rapamycin for up to 3 hours. A strain expressing Spt7 lacking the C-terminal 213aa, known as Spt7-217[33] also shows rapamycin resistant K14ac, suggesting that SLIK and SALSA are resistant to rapamycin (FIG. **1***e*). It is important to note that in this strain, the truncated Spt7 is expressed at levels similar to full length Spt7[33], hence the high levels of K14ac. Levels of truncated

Spt7 in SLIK and SALSA are normally much lower than full length Spt7 and make a minimal contribution to global levels of K14ac[22,23,25]. Moreover, this resistance to rapamycin is consistent with roles in the activated, but not basal, expression of TATA box genes[34] that function to promote growth when glucose is depleted[18,21] (FIG. **6**). Furthermore, this implicates the C-terminal 213aa of Spt7 in the rapamycin sensitivity of K14ac by SAGA as Spt8, a SAGA specific subunit, is recruited through this region[22,23]. Thus rapamycin may have differential effects on SAGA and SLIK/SALSA. SAGA is active in glucose grown cells while SLIK and SALSA are active in nutrient limited cells when TORC1 signalling is reduced (FIG. **6**).

The FY168 WT strain has been engineered to express only Spt7 containing a C-terminal truncation (FY571 Spt7-217) similar to that found naturally in the SLIK/SALSA complex. The Spt7 protein is expressed at similar level to full length Spt7[10]. we investigated levels of K14ac in this strain and the influence of Rtg2, the retrograde regulator and component of SLIK on the activity of this strain. FIG. **6***a* to shows that the K14ac is not significantly reduced in this strain when a deletion of RTG2 is introduced. Rtg2 is required for the H3 directed HAT activity of the SLIK complex[11]. This may reflect the naturally low levels of SLIK in cells compared to this complex. In addition we tested transcriptional responses (using reverse transcription coupled to real time PCR using primers to the loci indicated; No indicates reaction with no RTase added to reaction to control for DNA contamination) in this strain in exponential growth (log) and in early stationary phase (Stat or SP). Levels of transcript were normalised to U4snRNA. Levels of this transcript drop by half in stationary phase cells (data not shown). b Levels of RDNA transcription, monitored using a primer set to the intergenic region between the 25S and 18S regions, are reduced over 7 fold in stationary phase. c The retrograde responsive gene CIT2[12] is induced in the stationary phase cells and is dependent on Rtg2 in the WT Spt7(FY168) and Spt7-217 (FY571)backgrounds, as expected. d Induction of ACS1, encoding mitochondrial acetyl CoA synthase is induced in stationary phase and is Rtg2-dependent. In cells containing high levels of the SLIK/SALSA complex the gene is not induced. SLIK/SALSA may repress ACS1 expression or alternatively, the high levels of SLIK/SALSA may sequester Rtg2 creating an RTG2 null. e The induction of ATG1, a regulator of the autophagy[13], another starvation induced response, shows no dependence on Rtg2. Instead, the strains expressing Spt7-217 show a more than two fold increase in ATG1 mRNA levels under starvation conditions suggesting a role for the SALSA complex. The patterns of expression of these three genes may define how the SLIK/SALSA complexes contribute to gene regulation. We propose that ATG1 is dependent on SALSA and independent of SLIK and Rtg2. By contrast, CIT2 requires the SLIK complex for its activation while ACS1 is dependent on Rtg2 but not SLIK (The Rtg2 function to regulate nuclear uptake of Rtg1/3 as activators). Expression at a number of other loci is also monitored (f-i) in log phase. Modifications of lysines on histone H3 are monitored by Western blotting of total protein extracts using antibodies specific to the modification or protein indicated. n=2 for each experiment. Total protein and RNA were prepared from the same cultures for the experiment shown.

We used an N-terminally HA tagged version of Spt7 to examine its levels and integrity in rapamycin treated (FIG. **1***f*) or stationary phase cells (FIG. **7**). Reduced levels and C-terminal truncation of Spt7 occurs in both conditions and, by compromising the integrity of SAGA[23], explains the reduced K14ac. Thus the integrity of SAGA is controlled by C-terminal truncation of Spt7 that occurs when cells enter stationary phase or on rapamycin treatment. Levels of Gcn5, but not its RNA[18], also drop significantly in rapamycin treated WT cells (FIG. **1***g*). in contrast, Gcn5 levels are higher in rapamycin-treated cells expressing Spt7-217 (FIG. **1***h*). Thus the reduction in Gcn5 is likely to be a consequence of the C-terminal truncation and reduction in levels of Spt7.

SAGA Decreases with Age in Growing Cells

The data suggests that SAGA activity is a marker of growth and proliferation. As cells age both proliferative capacity and mitochondrial function are reduced. Experiments were undertaken to assess if SAGA changes during ageing by assessing levels in young cells (generally <5 generations old) compared to cells after 10 or 20 generations of growth. As cells age, levels of K14ac drop (FIG. **2***a*) and this is associated with an overall decrease in HA-Spt7 levels, in particular a drop in full length HA-Spt7 and increased truncated forms of HA-Spt7 supporting loss of SAGA function during ageing (FIG. **2***b*). By contrast, in the strain expressing only C-terminally truncated Spt7 (Spt7-217) K14ac does not drop in old cells (FIG. **2***c*). Total protein preparations were made from young cells or biotinylated cells after 20 generations of growth in exponential phase in rich medium, isolated using streptavidin magnetic beads. Western blot of levels of K14ac in total protein extracts prepared from FY168 (WT) and FY571 expressing Spt7-217. Levels of histone H3 were assessed to control for loading. It can be seen from FIG. **8** that there are differences in the amount of protein isolated. Levels of K14ac drop in the old WT strain but not in the strain expressing Spt7-217 suggesting that the C-terminal region of Spt7 is required for the reduction in K14ac and that SAGA is the target of this regulation. Note in this preparation there is less histone "clipping" evident than in other experiments (See FIG. **2***a*). These cells also contain increased levels of a smaller form of histone H3, possibly clipped[36]. This suggests that the mechanism by which SAGA and K14ac are reduced as cells age is similar to that occurring in rapamycin treated cells and involves processing of the C-terminal region of Spt7.

TORC1 F Maintains K14ac in Growing Cells

We sought to define how rapamycin influences acetylation by SAGA. There are four targets of rapamycin in yeast, Fpr1-4[37]. In the presence of rapamycin, Fpr1 inhibits functions associated with the PI3-related kinases Tor1 or Tor2 within the TORC1 complex[38]. This supports TORC1-dependent signalling controlling the global levels of K14ac, K18ac and K4me3 by maintaining SAGA function in proliferating cells. inhibition of TORC1 by rapamycin during the early stages of growth results in upregulation of SLIK/SALSA regulated genes that promote efficient respiration of glucose and stress resistance (FIG. **9**)[20,39]. As can be seen in FIG. **9***b*, levels of CIT2 expression, regulated by the TORC-1 complex are increased upon addition of rapamycin.

AMPK is generally considered to negatively regulate mammalian mTOR, resulting in down regulation of TORC1 signalling when glucose becomes scarce and intracellular levels of AMP increase[63]. The yeast AMPK Snf1 as can be seen from FIG. **10** may function in a similar way as it is required for the rapamycin-dependent reduction in K14ac (a). Levels of K14ac in a snf1Δ strain are reduced to about 50% of those in a WT strain, due to Snf1 directed phosphorylation of serine 10 on histone H3 that promotes K14 acetylation by Gcn5[64]. Importantly, K14ac (a) and Gcn5 (b) and some of the HA-Spt7 in the cell (c) are resistant to rapamycin in the snf1Δ strain. Note that track five* is under loaded in c. Note that the integrity of S10 on histone H3, phosphorylated by Snf1, does not influence the rapamycin sensitivity of K14ac although as with the snf1Δ, level of K14ac is reduced in this background

(d). We asked is Snf1 is functioning in the nucleus or cytoplasm. Gal83 is required for the nuclear uptake of Snf1[65] and HA tagged-Gal83 moves from the cytoplasm to the nucleus in rapamycin treated cells as demonstrated by indirect immunofluorescence in fixed cells (e). However, the relationship between Gal83 and Snf1 is not straightforward as gal83Δ strains show WT levels of K14ac in untreated cells and some resistance to rapamycin (f). Similar results are observed for Gcn5 protein in the gal83Δ strain (g). Thus it appears that Gal83 is required for the rapamycin dependent reduction in K14ac and Gcn5 suggesting that this is a nuclear function for Snf1.

SLIK Controls CLS Through Rtg2

We examined mitochondrial membrane potential (ψ) and CLS in the strain expressing only truncated Spt7 (Spt7-217), and thus expressing high levels of SLIK/SALSA complexes during exponential growth. Both ψ (FIG. **4***a*) and average CLS (FIG. **4***b*) are increased compared to WT but the strain then appears to undergo a rapid and complete loss of viability around day 12 in culture that may reflect imbalances in patterns of gene expression. Rtg2 is repressed by the TORC1 complex[26] and has at least two distinct functions, one as a regulator of retrograde response, and a second as a component of SLIK[13]. The high levels of truncated Spt7 might result in sequestration of Rtg2 into a SLIK complex, resulting in an rtg2 null for other functions. In support of this, an rtg2 strain shows increase ψ in exponential phase (FIG. **4***a*), increased mitochondrial protein synthesis (FIG. **4***c*) and enhanced CLS (FIG. **4***b*). This suggests that Rtg2 functions to repress mitochondrial function when TORC1 is active and that the formation of SLIK is linked to reduced TORC1 signalling, leading to truncation of Spt7 and relief of Rtg2-dependent repression of respiration. This provides an additional way to extend CLS. Interestingly, both Spt7 and Rtg2 are reported to be mitochondrially associated proteins[13,47]. Finally, we show that the most marked increase in CLS is observed when RTG2 is knocked out of FY571(Spt7-217) (FIG. **4***b*), perhaps reflecting strong induction of genes for autophagy, known to prolong lifespan, by SALSA, as this is Rtg2 independent. It should be noted that this rtgΔ phenotype can also be produced by the addition of inhibitors of mitochondrial respiration.

In summary, we show that the SAGA family of transcriptional regulators control the balance between growth and chronological lifespan. Metabolic changes resulting in up- or down-regulation of respiration are differentially controlled by TORC1 and Sch9 signalling to these complexes. TORC1 coordinates mitochondrial function with gene expression through the activities of Spt7 and Rtg2 and the chromatin modification at K14 on histone H3, providing a TORC1 signalling to SAGA and SLIK highly efficient mechanism by which cells switch fate in order to control the balance between growth and longevity.

Disruption of SAGA Results in Increased H3K18 Acetylation and an Extension in Chronological Lifespan.

FIG. **13** is a western blot showing the increase in H3K18 acetylation in strains in which the SAGA complex has been disrupted. As can be seen in the top rows of both panels, the amount of H3K18ac present in whole cell yeast extracts in stains in which the SAGA complex has been disrupted are increased compared to wildtype. The strains used in these experiments were either ΔSPT8 or Spt7 truncated.

FIG. **14** shows that *S. cerevisiae* strains having a disrupted SAGA complex have an increased chronological lifespan. As show in the figure strains FY631 and FY2030 are wild type, strain FY571 expresses a truncated Spt7 protein which lacks the SAGA specific Spt7 region, strain FY2037 is ΔSPT8 (Wu, P.Y. and Winston, F., Mol Cell Biol., 22(15), p5367-5379). Lifespan was determined as described in Murakami, C. and Kaeberlein, M., (2009) J. Vis. Exp., 27. Briefly, chronological lifespan of yeast refers to the profile of viability of an ageing yeast culture over time. A yeast culture is grown in liquid media until the glucose carbon source is exhausted and the cells stop dividing. At this point the proportion of cells which are alive and able to divide is measured by observing the outgrowth characteristics of a fresh inoculate of the aging culture using a Bioscreen C machine. Viabilities at various time points are compared to determine the chronological lifespan of the culture.

FIG. **15** shows that in a H3K18Q mutant in which acetylation at this position is disrupted chronological lifespan, as measured using the method above, is reduced compared to wild type. In the H3K18Q yeast strain, both endogenous copies of the H3 gene have been deleted and replaced by a single copy of the H3 gene containing a substitution of lysine 18 with glutamine. In the wild type strain shown in the figure, the deleted H3 genes have been replaced with a single wild type copy of the gene.

All publications mentioned in the above specification are herein incorporated by reference in their entirety. Various modifications and variations of the described methods and system of the present invention will be apparent to those skilled in the art without departing from the scope and spirit of the present invention. Although the present invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in biochemistry and biotechnology or related fields are intended to be with in the scope of the following claims.

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Sequence Listing

sch9

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Sch9
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Rtg2
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Tor1

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Tor1
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Ubp8

SEQ ID No: 9

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Ubp8
>YMR223W Chr 13

SEQ ID No: 10

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Spt7

SEQ ID No: 11

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Spt7
>YER081C Chr 2

SEQ ID No: 12

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SPT8

SEQ ID No: 13

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Spt8
>YLR055C Chr 12

SEQ ID No: 14

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Snf1

SEQ ID No: 15

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Snf1
YDR477W Chr 4

SEQ ID No: 16

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ACS1

SEQ ID No: 17

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 181 TYSMGVRKGD TVAVYMPMVP EAIITLLAIS RIGAIHSVVF AGFSSNSLRD RINDGDSKVV
 241 ITTDESNRGG KVIETKRIVD DALRETPGVR HVLVYRKTNN PSVAFHAPRD LDWATEKKKY
 301 KTYYPCTPVD SEDPLFLLYT SGSTGAPKGV QHSTAGYLLG ALLTMRYTFD THQEDVFFTA
 361 GDIGWITGHT YVVYGPLLYG CATLVFEGTP AYPNYSRYWD IIDEHKVTQF YVAPTALRLL
 421 KRAGDSYIEN HSLKSLRCLG SVGEPIAAEV WEWYSEKIGK NEIPIVDTYW QTESGSHLVT
 481 PLAGGVTPMK PGSASFPFFG IDAVVLDPNT GEELNTSHAE GVLAVKAAWP SFARTIWKNH
 541 DRYLDTYLNP YPGYYFTGDG AAKDKDGYIW ILGRVDDVVN VSGHRLSTAE IEAAIIEDPI
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Sequence Listing

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Acs1

>YAL054C Chr 1

SEQ ID No: 18

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Spt7-217

SEQ ID No: 19

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   61 YFLKGNIALN VEKSFPLTQE EEHHGAVSPA VDTRSDDVSS QTIKDNNNTN TNTSISNENH
  121 VENEIEDKGD NAIANEDNFV NNDESDNVEE DLFKLDLEDL KQQISGTRFI GNLSLKIRYV
  181 LWQCAIDYIY CDRNEFGDEN DTEYTLLDVE EKEEEEIGKN EKPQNKEGIS KFAEDEDYDD
  241 EDENYDEDST DVKNVDDPPK NLDSISSSNI EIDDERRLVL NISISKETLS KLKTNNVEEI
  301 MGNWNKIYHS FEYDKETMIK RLKLEESDKM IEKGKKKRSR SDLEAATDEQ DRENTNDEPD
  361 TNQKLPTPEG STFSDTGNKR PKQSNLDLTV NLGIENLSLK HLLSSIQQKK SQLGISDYEL
  421 KHLIMDVRKN RSKWTSDERI GQEELYEACE KVVLELRNYT EHSTPFLNKV SKREAPNYHQ
  481 IIKKSMDLNT VLKKLKSFQY DSKQEFVDDI MLIWKNCLTY NSDPSHFLRG HAIAMQKKSL
  541 QLIRMIPNIT IRNRADLEKE IEDMEKDKDY ELDEEEEVAG SGRKGLNMGA HMLAKENGKV
  601 SEKDSSKTVK DEAPTNDDKL TSVIPEGEKE KDKTASSTVT VHENVNKNEI KENGKNEEQD
  661 MVEESSKTED SSKDADAAKK DTEDGLQDKT AENKEAGENN EEEEDDDDED EDEDMVDSQS
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SPT7-217 DNA

SEQ ID No: 20

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Sequence Listing

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Spt3

SEQ ID No: 21

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 121 GEKDEKDGGN MMKVKKSQIK LPWELQFMFN EHPLENNDDN DDMDEDEREA NIVTLKRLKM
 181 ADDRTRNMTK EEYVHWSDCR QASFTFRKNK RFKDWSGISQ LTEGKPHDDV IDILGFLTFE
 241 IVCSLTETAL KIKQREQVLQ TQKDKSQQSS QDNTNFEFAS STLHRKKRLF DGPENVINPL
 301 KPRHIEEAWR VLQTIDMRHR ALTNFKGGRL SSKPIIM
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Spt3

SEQ ID No: 22

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SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 22

<210> SEQ ID NO 1
<211> LENGTH: 824
<212> TYPE: PRT
<213> ORGANISM: Saccharomyces cerevisiae

<400> SEQUENCE: 1

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Ser Ser Thr Ala Gly Asn Asp Asn Gly Tyr Pro Cys Lys Leu Val Ser
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Ala Met Gly Thr Thr Gly Ile Thr Ser Glu Asn Ala Leu Phe Gln Met
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Lys Ser Met Asn Asn Gly Ile Ser Ser Val Asn Asn Asn Asn Ser Asn
            100                 105                 110

Thr Pro Thr Ile Ile Thr Thr Ser Gln Glu Glu Thr Asn Ala Gly Asn
        115                 120                 125

Val His Gly Asp Thr Gly Gly Asn Ser Leu Gln Asn Ser Glu Asp Asp
    130                 135                 140

Asn Phe Ser Ser Ser Ser Thr Thr Lys Cys Leu Leu Ser Ser Thr Ser
145                 150                 155                 160

Ser Leu Ser Ile Asn Gln Arg Glu Ala Ala Ala Ala Ala Tyr Gly Pro
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Asp Thr Asp Ile Pro Arg Gly Lys Leu Glu Val Thr Ile Ile Glu Ala
            180                 185                 190

Arg Asp Leu Val Thr Arg Ser Lys Asp Ser Gln Pro Tyr Val Val Cys
        195                 200                 205

Thr Phe Glu Ser Ser Glu Phe Ile Ser Asn Gly Pro Glu Ser Leu Gly
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Ala Ile Asn Asn Asn Asn Asn Asn Asn Asn Asn Asn Gln His Asn Gln
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Asn Gln His Ile Asn Asn Asn Asn Glu Asn Thr Asn Pro Asp Ala Ala
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Ser Gln His His Asn Asn Asn Ser Gly Trp Asn Gly Ser Gln Leu Pro
            260                 265                 270

Ser Ile Lys Glu His Leu Lys Lys Lys Pro Leu Tyr Thr His Arg Ser
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Ser Ser Gln Leu Asp Gln Leu Asn Ser Cys Ser Ser Val Thr Asp Pro
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Ser Lys Arg Ser Ser Asn Ser Ser Ser Gly Ser Ser Asn Gly Pro Lys
305                 310                 315                 320

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Leu Ala His Ala Ser Gln His Gln Trp His Ser Leu Lys Pro Arg Val
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Ile Asp Glu Val Val Ser Gly Asp Ile Leu Ile Lys Trp Thr Tyr Lys
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    530                 535                 540

Leu Leu Asp Ala Asn Gly Asn Ile Ala Leu Cys Asp Phe Gly Leu Ser
545                 550                 555                 560

Lys Ala Asp Leu Lys Asp Arg Thr Asn Thr Phe Cys Gly Thr Thr Glu
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Tyr Leu Ala Pro Glu Leu Leu Leu Asp Glu Thr Gly Tyr Thr Lys Met
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Val Asp Phe Trp Ser Leu Gly Val Leu Ile Phe Glu Met Cys Cys Gly
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Trp Ser Pro Phe Phe Ala Glu Asn Asn Gln Lys Met Tyr Gln Lys Ile
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Ala Phe Gly Lys Val Lys Phe Pro Arg Asp Val Leu Ser Gln Glu Gly
625                 630                 635                 640

Arg Ser Phe Val Lys Gly Leu Leu Asn Arg Asn Pro Lys His Arg Leu
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Gly Ala Ile Asp Asp Gly Arg Glu Leu Arg Ala His Pro Phe Phe Ala
            660                 665                 670

Asp Ile Asp Trp Glu Ala Leu Lys Gln Lys Lys Ile Pro Pro Pro Phe
        675                 680                 685

Lys Pro His Leu Val Ser Glu Thr Asp Thr Ser Asn Phe Asp Pro Glu
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Phe Thr Thr Ala Ser Thr Ser Tyr Met Asn Lys His Gln Pro Met Met
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Thr Ala Thr Pro Leu Ser Pro Ala Met Gln Ala Lys Phe Ala Gly Phe
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Thr Phe Val Asp Glu Ser Ala Ile Asp Glu His Val Asn Asn Asn Arg
            740                 745                 750

Lys Phe Leu Gln Asn Ser Tyr Phe Met Glu Pro Gly Ser Phe Ile Pro
        755                 760                 765

Gly Asn Pro Asn Leu Pro Pro Asp Glu Asp Val Ile Asp Asp Asp Gly
    770                 775                 780

Asp Glu Asp Ile Asn Asp Gly Phe Asn Gln Glu Lys Asn Met Asn Asn
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Phe Val Ser Gly Arg Phe Glu Ile
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<211> LENGTH: 2475
<212> TYPE: DNA
<213> ORGANISM: Saccharomyces cerevisiae

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gagtcactag gcgccattaa taataacaac aataacaaca acaataatca gcataatcaa    720
aaccagcata ttaacaacaa caacgaaaat accaaccctg acgctgctag ccagcatcat    780
aataataaca gtggttggaa cggttctcag ttaccatcga taaaagagca cttgaagaaa    840
aaaccccttt atacacacag atcatcttcc caattagatc agctaaactc ttgctcttca    900
gtaaccgatc cgagcaaacg ttcttctaat tcttcgtcgg gttcttcaaa tggtccaaag    960
aatgatagtt cacatccaat atggcatcac aagacaacgt ttgatgtttt gggatctcac   1020
tcggaattag atatttctgt ttatgatgct gcccacgacc atatgttctt aggccaagtt   1080
agactgtatc caatgattca taatttagca catgcttccc aacaccaatg gcacagtttg   1140
aaacctcgcg ttattgatga agttgtgtcc ggtgatattt taatcaaatg gacttacaaa   1200
cagacaaaga aaagacatta tggcccacaa gattttgaag ttcttcgatt attgggtaag   1260
ggtacttttg gccaagtcta ccaagttaag aagaaagaca ctcaaagaat ttatgcaatg   1320
aaagttctct ccaagaaagt tattgtcaag aaaaatgaga tcgcccacac aattggcgaa   1380
agaaatatcc tagtcacgac agcgtccaaa tcgtccccat tcattgtcgg attgaagttt   1440
tcctttcaaa caccaacaga tctgtatttg gtcactgatt atatgagtgg tggagaatta   1500
ttctggcatt tacaaaagga gggccgtttt tcggaagaca gagcgaaatt ctatatcgct   1560
gagttagtcc tagcgttaga acatttacac gataacgata tcgtttacag ggacctaaag   1620
cctgaaaaca ttctactcga tgccaacggt aacatcgctc tttgcgattt tggtctttct   1680
aaagctgact tgaaggatag aacaaacaca ttttgcggca ccacggaata cctggcacca   1740
gaattgttac tggacgaaac cggctacacc aaaatggtcg atttctggtc tctaggtgtt   1800
ttgatatttg aaatgtgttg tggttggtcc cctttctttg cggaaaataa tcaaaaaatg   1860
taccaaaaaa ttgcctttgg taaagtcaaa ttccccagag acgtactgtc acaagagggg   1920
aggtcttttg taaagggttt actaaacaga aaccccaaac atagactcgg tgccattgat   1980
gatggaagag aactacgagc tcatccattt ttcgcagata tcgactggga ggccttgaag   2040
cagaaaaaaa ttccaccacc tttcaaacct cacctagtct cggagacgga tacctcgaat   2100
tttgacccag agttcacaac agcttcaact tcatacatga acaagcacca gccgatgatg   2160
actgctaccc cgctatctcc agccatgcaa gcaaagtttg ctggtttcac ctttgttgat   2220
gagtccgcca tcgatgaaca cgttaataac aacagaaaat tcctacaaaa ctcgtacttt   2280
atggaacctg gttcctttat cccgggaaat ccaaacttac ctccagacga agatgtcatc   2340
gatgatgacg gggacgagga catcaatgat ggattcaacc aagagaaaaa tatgaacaac   2400
agccattcgc agatggactt cgacggcgac caacacatgg atgacgaatt tgtcagtgga   2460
agattcgaaa tatga                                                    2475
```

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<210> SEQ ID NO 3
<211> LENGTH: 588
<212> TYPE: PRT
<213> ORGANISM: Saccharomyces cerevisiae

<400> SEQUENCE: 3

Met Ser Thr Leu Ser Asp Ser Asp Thr Glu Thr Glu Val Val Ser Arg
1 5 10 15

Asn Leu Cys Gly Ile Val Asp Ile Gly Ser Asn Gly Ile Arg Phe Ser
20 25 30

Ile Ser Ser Lys Ala Ala His His Ala Arg Ile Met Pro Cys Val Phe
35 40 45

Lys Asp Arg Val Gly Leu Ser Leu Tyr Glu Val Gln Tyr Asn Thr His
50 55 60

Thr Asn Ala Lys Cys Pro Ile Pro Arg Asp Ile Ile Lys Glu Val Cys
65 70 75 80

Ser Ala Met Lys Arg Phe Lys Leu Ile Cys Asp Asp Phe Gly Val Pro
85 90 95

Glu Thr Ser Val Arg Val Ile Ala Thr Glu Ala Thr Arg Asp Ala Ile
100 105 110

Asn Ala Asp Glu Phe Val Asn Ala Val Tyr Gly Ser Thr Gly Trp Lys
115 120 125

Val Glu Ile Leu Gly Gln Glu Asp Glu Thr Arg Val Gly Ile Tyr Gly
130 135 140

Val Val Ser Ser Phe Asn Thr Val Arg Gly Leu Tyr Leu Asp Val Ala
145 150 155 160

Gly Gly Ser Thr Gln Leu Ser Trp Val Ile Ser Ser His Gly Glu Val
165 170 175

Lys Gln Ser Ser Lys Pro Val Ser Leu Pro Tyr Gly Ala Gly Thr Leu
180 185 190

Leu Arg Arg Met Arg Thr Asp Asp Asn Arg Ala Leu Phe Tyr Glu Ile
195 200 205

Lys Glu Ala Tyr Lys Asp Ala Ile Glu Lys Ile Gly Ile Pro Gln Glu
210 215 220

Met Ile Asp Asp Ala Lys Lys Glu Gly Gly Phe Asp Leu Trp Thr Arg
225 230 235 240

Gly Gly Gly Leu Arg Gly Met Gly His Leu Leu Leu Tyr Gln Ser Glu
245 250 255

Gly Tyr Pro Ile Gln Thr Ile Ile Asn Gly Tyr Ala Cys Thr Tyr Glu
260 265 270

Glu Phe Ser Ser Met Ser Asp Tyr Leu Phe Leu Lys Gln Lys Ile Pro
275 280 285

Gly Ser Ser Lys Glu His Lys Ile Phe Lys Val Ser Asp Arg Arg Ala
290 295 300

Leu Gln Leu Pro Ala Val Gly Leu Phe Met Ser Ala Val Phe Glu Ala
305 310 315 320

Ile Pro Gln Ile Lys Ala Val His Phe Ser Glu Gly Gly Val Arg Glu
325 330 335

Gly Ser Leu Tyr Ser Leu Leu Pro Lys Glu Ile Arg Ala Gln Asp Pro
340 345 350

Leu Leu Ile Ala Ser Arg Pro Tyr Ala Pro Leu Leu Thr Glu Lys Tyr
355 360 365

Leu Tyr Leu Leu Arg Thr Ser Ile Pro Gln Glu Asp Ile Pro Glu Ile
370 375 380

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Val Asn Glu Arg Ile Ala Pro Ala Leu Cys Asn Leu Ala Phe Val His
385                 390                 395                 400

Ala Ser Tyr Pro Lys Glu Leu Gln Pro Thr Ala Ala Leu His Val Ala
                405                 410                 415

Thr Arg Gly Ile Ile Ala Gly Cys His Gly Leu Ser His Arg Ala Arg
            420                 425                 430

Ala Leu Ile Gly Ile Ala Leu Cys Ser Arg Trp Gly Gly Asn Ile Pro
        435                 440                 445

Glu Ser Glu Glu Lys Tyr Ser Gln Glu Leu Glu Gln Val Val Leu Arg
    450                 455                 460

Glu Gly Asp Lys Ala Glu Ala Leu Arg Ile Val Trp Trp Thr Lys Tyr
465                 470                 475                 480

Ile Gly Thr Ile Met Tyr Val Ile Cys Gly Val His Pro Gly Gly Asn
                485                 490                 495

Ile Arg Asp Asn Val Phe Asp Phe His Val Ser Lys Arg Ser Glu Val
            500                 505                 510

Glu Thr Ser Leu Lys Glu Leu Ile Ile Asp Asp Ala Asn Thr Thr Lys
        515                 520                 525

Val Lys Glu Glu Ser Thr Arg Lys Asn Arg Gly Tyr Glu Val Val Val
    530                 535                 540

Arg Ile Ser Lys Asp Asp Leu Lys Thr Ser Ala Ser Val Arg Ser Arg
545                 550                 555                 560

Ile Ile Thr Leu Gln Lys Lys Val Arg Lys Leu Ser Arg Gly Ser Val
                565                 570                 575

Glu Arg Val Lys Ile Gly Val Gln Phe Tyr Glu Glu
            580                 585
```

<210> SEQ ID NO 4
<211> LENGTH: 1767
<212> TYPE: DNA
<213> ORGANISM: Saccharomyces cerevisiae

<400> SEQUENCE: 4

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atgtcaacac ttagcgatag tgataccgag actgaggtcg tgtcgagaaa cttgtgtgga     60

atcgtcgaca taggttctaa tggtattcgt tttagtatat cttccaaggc tgcacatcat    120

gcaagaatta tgccttgtgt ttttaaagat agggttggtc tttctctata cgaagttcaa    180

tataatacac atacgaacgc aaaatgccct attcccagag atattataaa agaggtttgt    240

tctgccatga agagattcaa attaatttgc gatgattttg gtgtacctga aactagtgtc    300

agagtaattg caacagaagc cacgcgagat gctattaacg cggatgaatt tgttaatgct    360

gtttacggta gcactggctg gaaagtagaa atattaggcc aggaagatga aactagggtc    420

ggcatatatg gtgttgtttc ctcatttaat acagtaagag gtctatatct agatgtggca    480

ggtggtagta ctcagttatc atgggtaata agctcgcacg gagaagtcaa gcaatccagc    540

aaacctgtat ctttgccata tggagctgga actcttttga gaagaatgag aacagatgat    600

aatagggcac ttttttatga gattaaagaa gcgtacaaag atgcgattga aaaaattggt    660

atacctcaag aaatgattga tgacgccaag aaagaaggtg gatttgacct ttggacccgt    720

gggggtggtt taagaggtat gggacatctg cttctttacc agtcggaagg ttatcccatc    780

caaacaataa ttaacggata tgcttgcact tatgaagaat tctcgtctat gtcagattat    840

ctattcctaa aacaaaaaat accaggttct tcaaaagagc ataaaatatt taaggtttct    900

gatagaaggg ctttacaact tcctgccgtt ggtttgttca tgagtgctgt ttttgaagcg    960

attccccaga tcaaagctgt acattttagt gagggtggtg ttcgagaggg ttcactttat   1020
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tctcttcttc caaaagaaat tcgtgcacaa gatccattgc taattgcgtc ccgtccttat 1080

gctccattac ttactgaaaa atatctatat ctattgagaa catcaatccc acaagaagat 1140

ataccagaaa tagtaaacga aaggattgct cctgctttat gtaacttagc atttgttcat 1200

gcctcttatc caaaggagtt acaaccaaca gctgcattac atgttgctac aagagggata 1260

atagccggct gtcatggatt atctcacaga gctagagcgc tgataggaat tgctctatgt 1320

agtagatggg gcggcaacat tccggaatct gaagaaaaat actcccaaga attagaacaa 1380

gtagttctac gcgaaggtga taaagctgaa gcattgagaa ttgtatggtg gacgaagtat 1440

attggtacga ttatgtatgt gatttgcggt gttcatccag gtggtaatat cagagataac 1500

gtatttgatt tccatgtttc taagcgtagt gaggtggaga ccagtttaaa agaattaatc 1560

attgatgatg caaacactac aaaggtaaaa gaagaatcca cgcgtaaaaa tcgcgggtat 1620

gaagtggttg tgagaattag taaggacgat cttaaaacaa gtgcttccgt tcgttccaga 1680

attatcacgc tacaaaagaa agtacgcaag ctatctagag gaagtgtaga gagggttaaa 1740

attggcgtgc aattttatga agaataa 1767

<210> SEQ ID NO 5
<211> LENGTH: 439
<212> TYPE: PRT
<213> ORGANISM: Saccharomyces cerevisiae

<400> SEQUENCE: 5

Met Val Thr Lys His Gln Ile Glu Glu Asp His Leu Asp Gly Ala Thr
1 5 10 15

Thr Asp Pro Glu Val Lys Arg Val Lys Leu Glu Asn Asn Val Glu Glu
20 25 30

Ile Gln Pro Glu Gln Ala Glu Thr Asn Lys Gln Glu Gly Thr Asp Lys
35 40 45

Glu Asn Lys Gly Lys Phe Glu Lys Glu Thr Glu Arg Ile Gly Gly Ser
50 55 60

Glu Val Val Thr Asp Val Glu Lys Gly Ile Val Lys Phe Glu Phe Asp
65 70 75 80

Gly Val Glu Tyr Thr Phe Lys Glu Arg Pro Ser Val Val Glu Glu Asn
85 90 95

Glu Gly Lys Ile Glu Phe Arg Val Val Asn Asn Asp Asn Thr Lys Glu
100 105 110

Asn Met Met Val Leu Thr Gly Leu Lys Asn Ile Phe Gln Lys Gln Leu
115 120 125

Pro Lys Met Pro Lys Glu Tyr Ile Ala Arg Leu Val Tyr Asp Arg Ser
130 135 140

His Leu Ser Met Ala Val Ile Arg Lys Pro Leu Thr Val Val Gly Gly
145 150 155 160

Ile Thr Tyr Arg Pro Phe Asp Lys Arg Glu Phe Ala Glu Ile Val Phe
165 170 175

Cys Ala Ile Ser Ser Thr Glu Gln Val Arg Gly Tyr Gly Ala His Leu
180 185 190

Met Asn His Leu Lys Asp Tyr Val Arg Asn Thr Ser Asn Ile Lys Tyr
195 200 205

Phe Leu Thr Tyr Ala Asp Asn Tyr Ala Ile Gly Tyr Phe Lys Lys Gln
210 215 220

Gly Phe Thr Lys Glu Ile Thr Leu Asp Lys Ser Ile Trp Met Gly Tyr
225 230 235 240

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Ile Lys Asp Tyr Glu Gly Gly Thr Leu Met Gln Cys Ser Met Leu Pro
                245                 250                 255

Arg Ile Arg Tyr Leu Asp Ala Gly Lys Ile Leu Leu Leu Gln Glu Ala
            260                 265                 270

Ala Leu Arg Arg Lys Ile Arg Thr Ile Ser Lys Ser His Ile Val Arg
        275                 280                 285

Pro Gly Leu Glu Gln Phe Lys Asp Leu Asn Asn Ile Lys Pro Ile Asp
    290                 295                 300

Pro Met Thr Ile Pro Gly Leu Lys Glu Ala Gly Trp Thr Pro Glu Met
305                 310                 315                 320

Asp Ala Leu Ala Gln Arg Pro Lys Arg Gly Pro His Asp Ala Ala Ile
                325                 330                 335

Gln Asn Ile Leu Thr Glu Leu Gln Asn His Ala Ala Ala Trp Pro Phe
            340                 345                 350

Leu Gln Pro Val Asn Lys Glu Glu Val Pro Asp Tyr Tyr Asp Phe Ile
        355                 360                 365

Lys Glu Pro Met Asp Leu Ser Thr Met Glu Ile Lys Leu Glu Ser Asn
    370                 375                 380

Lys Tyr Gln Lys Met Glu Asp Phe Ile Tyr Asp Ala Arg Leu Val Phe
385                 390                 395                 400

Asn Asn Cys Arg Met Tyr Asn Gly Glu Asn Thr Ser Tyr Tyr Lys Tyr
                405                 410                 415

Ala Asn Arg Leu Glu Lys Phe Phe Asn Asn Lys Val Lys Glu Ile Pro
            420                 425                 430

Glu Tyr Ser His Leu Ile Asp
        435


<210> SEQ ID NO 6
<211> LENGTH: 2128
<212> TYPE: DNA
<213> ORGANISM: Saccharomyces cerevisiae

<400> SEQUENCE: 6

tcttaaacac ttatgggcag caaaaaatgc gtctttcttc cctcgtctgt tgttttatgt     60

agggcgtaat gatgtttgct tgtcaacaaa tgaatacgta cagaagagaa ttctagccaa    120

ggcaattatt gcatactgca agtactgagt acgttaacgt tgctagaata acattaaatg    180

agatgtagca atgcagatcc ttcctcagta ggcttaatgc tccactagaa tttttgacca    240

gccactattt gctttttttcg caatcctttt caatactcga gagcaaagac aaaaaaaata    300

agacatgtag tgcgctgtat ggaaaagaat taattagaac tttacaaacg cgtgttaaac    360

aggcatattt aagtgtttgg acctaaacaa tatatcgact attgaaattc ttacgcaaga    420

ttttttatag ttggatattc atatattctt acaactctct ctactttcag ttttttgaag    480

ctatatgtat cattatatac gtttatggat ttttcaaacc taaacaatta tactgcgtaa    540

atgtttgatt aagcaataaa taaaaacaaa ggattggtaa gggaagaccg tgagccgccc    600

aaaagtcttc agttaactca ggttcgtatt ctacattaga tggtcacaaa acatcagatt    660

gaagaggatc acttggatgg agctacgacg gatcccgaag ttaaacgggt aaaattagaa    720

aacaacgttg aagaaataca acctgagcag gctgagacca ataaacaaga gggcaccgat    780

aaagagaata aaggaaagtt cgagaaagaa actgagagaa taggaggatc tgaagtggtt    840

acagatgtgg aaaaaggaat tgtcaaattt gaatttgatg gtgttgaata cacattcaaa    900

gagagaccca gtgtcgtaga ggaaaatgaa ggtaaaattg agtttagggt ggtgaataat    960

gataatacta aagaaaacat gatggtccta actggattaa aaaacatttt tcaaaagcaa   1020
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ttaccaaaaa tgcccaaaga atacattgcc aggttagtct atgatcgaag tcatctttcc   1080

atggctgtca ttaggaagcc attgactgtc gtaggtggca taacatatcg acctttcgat   1140

aagagagaat tcgcagaaat tgttttctgt gccatcagtt cgacggaaca ggtacgcggt   1200

tatggtgcgc atctaatgaa tcacttaaaa gactatgtta gaaatacctc gaacataaaa   1260

tatttttga catatgcaga taattacgct attggatact ttaaaaagca aggcttcact   1320

aaagaaatca cgttggataa aagtatatgg atgggatata ttaaagatta tgaaggtggt   1380

acgctgatgc aatgttctat gttaccaaga atacgatatt tggacgcagg taagattcta   1440

ttattacaag aagcggccct gcgaagaaaa ataagaacga tttcgaaatc gcatattgta   1500

aggcctggtt tagagcaatt caaagactta aacaatatca aaccgattga tccaatgact   1560

attcctggct tgaaagaagc cggctggact cccgagatgg atgcgttggc acaacgtccc   1620

aagcgtggtc cacacgatgc agcaatacag aatatactca cagagctaca aaatcatgca   1680

gcagcttggc ccttcttaca acccgttaat aaagaggagg tccccgacta ttatgatttt   1740

atcaaagagc caatggactt gagcaccatg gaaataaaat tagagagcaa caaatatcag   1800

aagatggaag acttcatata tgatgccaga ttggtgttta acaattgccg aatgtacaat   1860

ggcgagaata cgtcgtatta caagtatgct aataggctag agaaattctt caataataaa   1920

gtaaaagaaa tacctgaata ttctcacctt attgattaat gcgtagaaga agcttttccg   1980

ctactattcc tttcgaagaa gaaataaatg tttagtacgg cgagacgatg tgatcaattg   2040

aggttatttt actacttttc ctttcatttt tgtaaggttt tctttctttg ttagtgtgac   2100

gttggtattt acctttatgt aactatat                                      2128
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<210> SEQ ID NO 7
<211> LENGTH: 2470
<212> TYPE: PRT
<213> ORGANISM: Saccharomyces cerevisiae

<400> SEQUENCE: 7

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Met Glu Pro His Glu Glu Gln Ile Trp Lys Ser Lys Leu Leu Lys Ala
1               5                   10                  15

Ala Asn Asn Asp Met Asp Met Asp Arg Asn Val Pro Leu Ala Pro Asn
            20                  25                  30

Leu Asn Val Asn Met Asn Met Lys Met Asn Ala Ser Arg Asn Gly Asp
        35                  40                  45

Glu Phe Gly Leu Thr Ser Ser Arg Phe Asp Gly Val Val Ile Gly Ser
    50                  55                  60

Asn Gly Asp Val Asn Phe Lys Pro Ile Leu Glu Lys Ile Phe Arg Glu
65                  70                  75                  80

Leu Thr Ser Asp Tyr Lys Glu Glu Arg Lys Leu Ala Ser Ile Ser Leu
                85                  90                  95

Phe Asp Leu Leu Val Ser Leu Glu His Glu Leu Ser Ile Glu Glu Phe
            100                 105                 110

Gln Ala Val Ser Asn Asp Ile Asn Asn Lys Ile Leu Glu Leu Val His
        115                 120                 125

Thr Lys Lys Thr Ser Thr Arg Val Gly Ala Val Leu Ser Ile Asp Thr
    130                 135                 140

Leu Ile Ser Phe Tyr Ala Tyr Thr Glu Arg Leu Pro Asn Glu Thr Ser
145                 150                 155                 160

Arg Leu Ala Gly Tyr Leu Arg Gly Leu Ile Pro Ser Asn Asp Val Glu
                165                 170                 175
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Val Met Arg Leu Ala Ala Lys Thr Leu Gly Lys Leu Ala Val Pro Gly
            180                 185                 190

Gly Thr Tyr Thr Ser Asp Phe Val Glu Phe Glu Ile Lys Ser Cys Leu
        195                 200                 205

Glu Trp Leu Thr Ala Ser Thr Glu Lys Asn Ser Phe Ser Ser Ser Lys
    210                 215                 220

Pro Asp His Ala Lys His Arg Ala Leu Leu Ile Ile Thr Ala Leu Ala
225                 230                 235                 240

Glu Asn Cys Pro Tyr Leu Leu Tyr Gln Tyr Leu Asn Ser Ile Leu Asp
                245                 250                 255

Asn Ile Trp Arg Ala Leu Arg Asp Pro His Leu Val Ile Arg Ile Asp
            260                 265                 270

Ala Ser Ile Thr Leu Ala Lys Cys Leu Ser Thr Leu Arg Asn Arg Asp
        275                 280                 285

Pro Gln Leu Thr Ser Gln Trp Val Gln Arg Leu Ala Thr Ser Cys Glu
    290                 295                 300

Tyr Gly Phe Gln Val Asn Thr Leu Glu Cys Ile His Ala Ser Leu Leu
305                 310                 315                 320

Val Tyr Lys Glu Ile Leu Phe Leu Lys Asp Pro Phe Leu Asn Gln Val
                325                 330                 335

Phe Asp Gln Met Cys Leu Asn Cys Ile Ala Tyr Glu Asn His Lys Ala
            340                 345                 350

Lys Met Ile Arg Glu Lys Ile Tyr Gln Ile Val Pro Leu Leu Ala Ser
        355                 360                 365

Phe Asn Pro Gln Leu Phe Ala Gly Lys Tyr Leu His Gln Ile Met Asp
    370                 375                 380

Asn Tyr Leu Glu Ile Leu Thr Asn Ala Pro Ala Lys Lys Ile Pro His
385                 390                 395                 400

Leu Lys Asp Asp Lys Pro Gln Ile Leu Ile Ser Ile Gly Asp Ile Ala
                405                 410                 415

Tyr Glu Val Gly Pro Asp Ile Ala Pro Tyr Val Lys Gln Ile Leu Asp
            420                 425                 430

Tyr Ile Glu His Asp Leu Gln Thr Lys Phe Lys Phe Arg Lys Lys Phe
        435                 440                 445

Glu Asn Glu Ile Phe Tyr Cys Ile Gly Arg Leu Ala Val Pro Leu Gly
    450                 455                 460

Pro Val Leu Gly Lys Leu Leu Asn Arg Asn Ile Leu Asp Leu Met Phe
465                 470                 475                 480

Lys Cys Pro Leu Ser Asp Tyr Met Gln Glu Thr Phe Gln Ile Leu Thr
                485                 490                 495

Glu Arg Ile Pro Ser Leu Gly Pro Lys Ile Asn Asp Glu Leu Leu Asn
            500                 505                 510

Leu Val Cys Ser Thr Leu Ser Gly Thr Pro Phe Ile Gln Pro Gly Ser
        515                 520                 525

Pro Met Glu Ile Pro Ser Phe Ser Arg Glu Arg Ala Arg Glu Trp Arg
    530                 535                 540

Asn Lys Ser Ile Leu Gln Lys Thr Gly Glu Ser Asn Asp Asp Asn Asn
545                 550                 555                 560

Asp Ile Lys Ile Ile Ile Gln Ala Phe Arg Met Leu Lys Asn Ile Lys
                565                 570                 575

Ser Arg Phe Ser Leu Val Glu Phe Val Arg Ile Val Ala Leu Ser Tyr
            580                 585                 590

Ile Glu His Thr Asp Pro Arg Val Arg Lys Leu Ala Ala Leu Thr Ser
        595                 600                 605
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Cys Glu Ile Tyr Val Lys Asp Asn Ile Cys Lys Gln Thr Ser Leu His
    610                 615                 620

Ser Leu Asn Thr Val Ser Glu Val Leu Ser Lys Leu Leu Ala Ile Thr
625                 630                 635                 640

Ile Ala Asp Pro Leu Gln Asp Ile Arg Leu Glu Val Leu Lys Asn Leu
                645                 650                 655

Asn Pro Cys Phe Asp Pro Gln Leu Ala Gln Pro Asp Asn Leu Arg Leu
            660                 665                 670

Leu Phe Ile Ala Leu His Asp Glu Ser Phe Asn Ile Gln Ser Val Ala
        675                 680                 685

Met Glu Leu Val Gly Arg Leu Ser Ser Val Asn Pro Ala Tyr Val Ile
    690                 695                 700

Pro Ser Ile Arg Lys Ile Leu Leu Glu Leu Leu Thr Lys Leu Lys Phe
705                 710                 715                 720

Ser Thr Ser Ser Arg Glu Lys Glu Glu Thr Ala Ser Leu Leu Cys Thr
                725                 730                 735

Leu Ile Arg Ser Ser Lys Asp Val Ala Lys Pro Tyr Ile Glu Pro Leu
            740                 745                 750

Leu Asn Val Leu Leu Pro Lys Phe Gln Asp Thr Ser Ser Thr Val Ala
        755                 760                 765

Ser Thr Ala Leu Arg Thr Ile Gly Glu Leu Ser Val Val Gly Gly Glu
    770                 775                 780

Asp Met Lys Ile Tyr Leu Lys Asp Leu Phe Pro Leu Ile Ile Lys Thr
785                 790                 795                 800

Phe Gln Asp Gln Ser Asn Ser Phe Lys Arg Glu Ala Ala Leu Lys Ala
                805                 810                 815

Leu Gly Gln Leu Ala Ala Ser Ser Gly Tyr Val Ile Asp Pro Leu Leu
            820                 825                 830

Asp Tyr Pro Glu Leu Leu Gly Ile Leu Val Asn Ile Leu Lys Thr Glu
        835                 840                 845

Asn Ser Gln Asn Ile Arg Arg Gln Thr Val Thr Leu Ile Gly Ile Leu
    850                 855                 860

Gly Ala Ile Asp Pro Tyr Arg Gln Lys Glu Arg Glu Val Thr Ser Thr
865                 870                 875                 880

Thr Asp Ile Ser Thr Glu Gln Asn Ala Pro Pro Ile Asp Ile Ala Leu
                885                 890                 895

Leu Met Gln Gly Met Ser Pro Ser Asn Asp Glu Tyr Tyr Thr Thr Val
            900                 905                 910

Val Ile His Cys Leu Leu Lys Ile Leu Lys Asp Pro Ser Leu Ser Ser
        915                 920                 925

Tyr His Thr Ala Val Ile Gln Ala Ile Met His Ile Phe Gln Thr Leu
    930                 935                 940

Gly Leu Lys Cys Val Ser Phe Leu Asp Gln Ile Ile Pro Thr Ile Leu
945                 950                 955                 960

Asp Val Met Arg Thr Cys Ser Gln Ser Leu Leu Glu Phe Tyr Phe Gln
                965                 970                 975

Gln Leu Cys Ser Leu Ile Ile Ile Val Arg Gln His Ile Arg Pro His
            980                 985                 990

Val Asp Ser Ile Phe Gln Ala Ile  Lys Asp Phe Ser Ser  Val Ala Lys
        995                 1000                1005

Leu Gln  Ile Thr Leu Val Ser  Val Ile Glu Ala Ile  Ser Lys Ala
    1010                1015                1020

Leu Glu  Gly Glu Phe Lys Arg  Leu Val Pro Leu Thr  Leu Thr Leu
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    1025                1030                1035

Phe Leu  Val Ile Leu Glu Asn  Asp Lys Ser Ser Asp  Lys Val Leu
    1040                1045                1050

Ser Arg  Arg Val Leu Arg Leu  Leu Glu Ser Phe Gly  Pro Asn Leu
    1055                1060                1065

Glu Gly  Tyr Ser His Leu Ile  Thr Pro Lys Ile Val  Gln Met Ala
    1070                1075                1080

Glu Phe  Thr Ser Gly Asn Leu  Gln Arg Ser Ala Ile  Ile Thr Ile
    1085                1090                1095

Gly Lys  Leu Ala Lys Asp Val  Asp Leu Phe Glu Met  Ser Ser Arg
    1100                1105                1110

Ile Val  His Ser Leu Leu Arg  Val Leu Ser Ser Thr  Thr Ser Asp
    1115                1120                1125

Glu Leu  Ser Lys Val Ile Met  Asn Thr Leu Ser Leu  Leu Leu Ile
    1130                1135                1140

Gln Met  Gly Thr Ser Phe Ala  Ile Phe Ile Pro Val  Ile Asn Glu
    1145                1150                1155

Val Leu  Met Lys Lys His Ile  Gln His Thr Ile Tyr  Asp Asp Leu
    1160                1165                1170

Thr Asn  Arg Ile Leu Asn Asn  Asp Val Leu Pro Thr  Lys Ile Leu
    1175                1180                1185

Glu Ala  Asn Thr Thr Asp Tyr  Lys Pro Ala Glu Gln  Met Glu Ala
    1190                1195                1200

Ala Asp  Ala Gly Val Ala Lys  Leu Pro Ile Asn Gln  Ser Val Leu
    1205                1210                1215

Lys Ser  Ala Trp Asn Ser Ser  Gln Gln Arg Thr Lys  Glu Asp Trp
    1220                1225                1230

Gln Glu  Trp Ser Lys Arg Leu  Ser Ile Gln Leu Leu  Lys Glu Ser
    1235                1240                1245

Pro Ser  His Ala Leu Arg Ala  Cys Ser Asn Leu Ala  Ser Met Tyr
    1250                1255                1260

Tyr Pro  Leu Ala Lys Glu Leu  Phe Asn Thr Ala Phe  Ala Cys Val
    1265                1270                1275

Trp Thr  Glu Leu Tyr Ser Gln  Tyr Gln Glu Asp Leu  Ile Glu Ser
    1280                1285                1290

Leu Cys  Ile Ala Leu Ser Ser  Pro Leu Asn Pro Pro  Glu Ile His
    1295                1300                1305

Gln Thr  Leu Leu Asn Leu Val  Glu Phe Met Glu His  Asp Asp Lys
    1310                1315                1320

Ala Leu  Pro Ile Pro Thr Gln  Ser Leu Gly Glu Tyr  Ala Glu Arg
    1325                1330                1335

Cys His  Ala Tyr Ala Lys Ala  Leu His Tyr Lys Glu  Ile Lys Phe
    1340                1345                1350

Ile Lys  Glu Pro Glu Asn Ser  Thr Ile Glu Ser Leu  Ile Ser Ile
    1355                1360                1365

Asn Asn  Gln Leu Asn Gln Thr  Asp Ala Ala Ile Gly  Ile Leu Lys
    1370                1375                1380

His Ala  Gln Gln His His Ser  Leu Gln Leu Lys Glu  Thr Trp Phe
    1385                1390                1395

Glu Lys  Leu Glu Arg Trp Glu  Asp Ala Leu His Ala  Tyr Asn Glu
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Arg Glu  Lys Ala Gly Asp Thr  Ser Val Ser Val Thr  Leu Gly Lys
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Met Arg  Ser Leu His Ala Leu  Ala Glu Trp Glu Gln  Leu Ser Gln
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Leu Ala  Ala Arg Lys Trp Lys  Val Ser Lys Leu Gln  Thr Lys Lys
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Leu Ile  Ala Pro Leu Ala Ala  Gly Ala Arg Gly Gly  Ser Gly Glu
    1460                1465                1470

Trp Asp  Met Leu Asp Glu Tyr  Ile Ser Val Met Lys  Pro Lys Ser
    1475                1480                1485

Pro Asp  Lys Glu Phe Phe Asp  Ala Ile Leu Tyr Leu  His Lys Asn
    1490                1495                1500

Asp Tyr  Asp Asn Ala Ser Lys  His Ile Leu Asn Ala  Arg Asp Leu
    1505                1510                1515

Leu Val  Thr Glu Ile Ser Ala  Leu Ile Asn Glu Ser  Tyr Asn Arg
    1520                1525                1530

Ala Tyr  Ser Val Ile Val Arg  Thr Gln Ile Ile Thr  Glu Phe Glu
    1535                1540                1545

Glu Ile  Ile Lys Tyr Lys Gln  Leu Pro Pro Asn Ser  Glu Lys Lys
    1550                1555                1560

Leu His  Tyr Gln Asn Leu Trp  Thr Lys Arg Leu Leu  Gly Cys Gln
    1565                1570                1575

Lys Asn  Val Asp Leu Trp Gln  Arg Val Leu Arg Ile  Arg Ser Leu
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Val Ile  Lys Pro Lys Gln Asp  Leu Gln Ile Trp Ile  Lys Phe Ala
    1595                1600                1605

Asn Leu  Cys Arg Lys Ser Gly  Arg Met Arg Leu Ala  Asn Lys Ala
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Leu Asn  Met Leu Leu Glu Gly  Gly Thr Ile Leu Val  Tyr Gln Ile
    1625                1630                1635

Arg Ser  Lys Pro Pro Pro Pro  Val Val Tyr Ala Gln  Leu Lys Tyr
    1640                1645                1650

Ile Trp  Ala Thr Gly Ala Tyr  Lys Glu Ala Leu Asn  His Leu Ile
    1655                1660                1665

Gly Phe  Thr Ser Arg Leu Ala  His Asp Leu Gly Leu  Asp Pro Asn
    1670                1675                1680

Asn Met  Ile Ala Gln Ser Val  Lys Leu Ser Ser Ala  Ser Thr Ala
    1685                1690                1695

Pro Tyr  Val Glu Glu Tyr Thr  Lys Leu Leu Ala Arg  Cys Phe Leu
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Lys Gln  Gly Glu Trp Arg Ile  Ala Thr Gln Pro Asn  Trp Arg Asn
    1715                1720                1725

Thr Asn  Pro Asp Ala Ile Leu  Gly Ser Tyr Leu Leu  Ala Thr His
    1730                1735                1740

Phe Asp  Lys Asn Trp Tyr Lys  Ala Trp His Asn Trp  Ala Leu Ala
    1745                1750                1755

Asn Phe  Glu Val Ile Ser Met  Val Gln Glu Glu Thr  Lys Leu Asn
    1760                1765                1770

Gly Gly  Lys Asn Asp Asp Asp  Asp Asp Thr Ala Val  Asn Asn Asp
    1775                1780                1785

Asn Val  Arg Ile Asp Gly Ser  Ile Leu Gly Ser Gly  Ser Leu Thr
    1790                1795                1800

Ile Asn  Gly Asn Arg Tyr Pro  Leu Glu Leu Ile Gln  Arg His Val
    1805                1810                1815

Val Pro  Ala Ile Lys Gly Phe  Phe His Ser Ile Ser  Leu Leu Glu
    1820                1825                1830
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Thr Ser  Cys Leu Gln Asp Thr  Leu Arg Leu Ser Thr  Leu Leu Phe
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Asn Phe  Gly Gly Ile Lys Glu  Val Ser Gln Ala Met  Tyr Glu Gly
    1850                 1855                 1860

Phe Asn  Leu Met Lys Ile Glu  Asn Trp Leu Glu Val  Leu Pro Gln
    1865                 1870                 1875

Leu Ile  Ser Arg Ile His Gln  Pro Asp Pro Thr Val  Ser Asn Ser
    1880                 1885                 1890

Leu Leu  Ser Leu Leu Ser Asp  Leu Gly Lys Ala His  Pro Gln Ala
    1895                 1900                 1905

Leu Val  Tyr Pro Leu Thr Val  Ala Ile Lys Ser Glu  Ser Val Ser
    1910                 1915                 1920

Arg Gln  Lys Ala Ala Leu Ser  Ile Ile Glu Lys Ile  Arg Ile His
    1925                 1930                 1935

Ser Pro  Val Leu Val Asn Gln  Ala Glu Leu Val Ser  His Glu Leu
    1940                 1945                 1950

Ile Arg  Val Ala Val Leu Trp  His Glu Leu Trp Tyr  Glu Gly Leu
    1955                 1960                 1965

Glu Asp  Ala Ser Arg Gln Phe  Phe Val Glu His Asn  Ile Glu Lys
    1970                 1975                 1980

Met Phe  Ser Thr Leu Glu Pro  Leu His Lys His Leu  Gly Asn Glu
    1985                 1990                 1995

Pro Gln  Thr Leu Ser Glu Val  Ser Phe Gln Lys Ser  Phe Gly Arg
    2000                 2005                 2010

Asp Leu  Asn Asp Ala Tyr Glu  Trp Leu Asn Asn Tyr  Lys Lys Ser
    2015                 2020                 2025

Lys Asp  Ile Asn Asn Leu Asn  Gln Ala Trp Asp Ile  Tyr Tyr Asn
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Val Phe  Arg Lys Ile Thr Arg  Gln Ile Pro Gln Leu  Gln Thr Leu
    2045                 2050                 2055

Asp Leu  Gln His Val Ser Pro  Gln Leu Leu Ala Thr  His Asp Leu
    2060                 2065                 2070

Glu Leu  Ala Val Pro Gly Thr  Tyr Phe Pro Gly Lys  Pro Thr Ile
    2075                 2080                 2085

Arg Ile  Ala Lys Phe Glu Pro  Leu Phe Ser Val Ile  Ser Ser Lys
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Gln Arg  Pro Arg Lys Phe Ser  Ile Lys Gly Ser Asp  Gly Lys Asp
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Tyr Lys  Tyr Val Leu Lys Gly  His Glu Asp Ile Arg  Gln Asp Ser
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Leu Val  Met Gln Leu Phe Gly  Leu Val Asn Thr Leu  Leu Lys Asn
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Asp Ser  Glu Cys Phe Lys Arg  His Leu Asp Ile Gln  Gln Tyr Pro
    2150                 2155                 2160

Ala Ile  Pro Leu Ser Pro Lys  Ser Gly Leu Leu Gly  Trp Val Pro
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Asn Ser  Asp Thr Phe His Val  Leu Ile Arg Glu His  Arg Asp Ala
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Lys Lys  Ile Pro Leu Asn Ile  Glu His Trp Val Met  Leu Gln Met
    2195                 2200                 2205

Ala Pro  Asp Tyr Glu Asn Leu  Thr Leu Leu Gln Lys  Ile Glu Val
    2210                 2215                 2220

Phe Thr  Tyr Ala Leu Asp Asn  Thr Lys Gly Gln Asp  Leu Tyr Lys
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Arg Thr  Thr Tyr Thr Arg Ser  Leu Ala Val Met Ser  Met Thr Gly
    2255                2260                2265

Tyr Ile  Leu Gly Leu Gly Asp  Arg His Pro Ser Asn  Leu Met Leu
    2270                2275                2280

Asp Arg  Ile Thr Gly Lys Val  Ile His Ile Asp Phe  Gly Asp Cys
    2285                2290                2295

Phe Glu  Ala Ala Ile Leu Arg  Glu Lys Tyr Pro Glu  Lys Val Pro
    2300                2305                2310

Phe Arg  Leu Thr Arg Met Leu  Thr Tyr Ala Met Glu  Val Ser Gly
    2315                2320                2325

Ile Glu  Gly Ser Phe Arg Ile  Thr Cys Glu Asn Val  Met Arg Val
    2330                2335                2340

Leu Arg  Asp Asn Lys Glu Ser  Leu Met Ala Ile Leu  Glu Ala Phe
    2345                2350                2355

Ala Leu  Asp Pro Leu Ile His  Trp Gly Phe Asp Leu  Pro Pro Gln
    2360                2365                2370

Lys Leu  Thr Glu Gln Thr Gly  Ile Pro Leu Pro Leu  Ile Asn Pro
    2375                2380                2385

Ser Glu  Leu Leu Arg Lys Gly  Ala Ile Thr Val Glu  Glu Ala Ala
    2390                2395                2400

Asn Met  Glu Ala Glu Gln Gln  Asn Glu Thr Arg Asn  Ala Arg Ala
    2405                2410                2415

Met Leu  Val Leu Arg Arg Ile  Thr Asp Lys Leu Thr  Gly Asn Asp
    2420                2425                2430

Ile Lys  Arg Phe Asn Glu Leu  Asp Val Pro Glu Gln  Val Asp Lys
    2435                2440                2445

Leu Ile  Gln Gln Ala Thr Ser  Ile Glu Arg Leu Cys  Gln His Tyr
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<210> SEQ ID NO 8
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<212> TYPE: PRT
<213> ORGANISM: Saccharomyces cerevisiae

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Ile Gly His Ile Phe Gly Ile Asn Ser Asn Asn Gly Leu Leu Phe Cys
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Phe Lys Cys Glu Asp Tyr Ile Gly Asn Ile Asp Leu Ile Asn Asp Ala
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Ile Leu Ala Lys Tyr Trp Asp Asp Val Cys Thr Lys Thr Met Val Pro
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Ser Met Glu Arg Arg Asp Gly Leu Ser Gly Leu Ile Asn Met Gly Ser
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Thr Cys Phe Met Ser Ser Ile Leu Gln Cys Leu Ile His Asn Pro Tyr
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Phe Ile Arg His Ser Met Ser Gln Ile His Ser Asn Asn Cys Lys Val
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Arg Ser Pro Asp Lys Cys Phe Ser Cys Ala Leu Asp Lys Ile Val His
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Glu Leu Tyr Gly Ala Leu Asn Thr Lys Gln Ala Ser Ser Ser Ser Thr
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Ser Thr Asn Arg Gln Thr Gly Phe Ile Tyr Leu Leu Thr Cys Ala Trp
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Lys Ile Asn Gln Asn Leu Ala Gly Tyr Ser Gln Gln Asp Ala His Glu
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Cys Pro Gly Cys Gln Asn Asn Ser Lys Thr Thr Ile Asp Pro Phe Leu
    290                 295                 300

Asp Leu Ser Leu Asp Ile Lys Asp Lys Lys Lys Leu Tyr Glu Cys Leu
305                 310                 315                 320

Asp Ser Phe His Lys Lys Glu Gln Leu Lys Asp Phe Asn Tyr His Cys
                325                 330                 335

Gly Glu Cys Asn Ser Thr Gln Asp Ala Ile Lys Gln Leu Gly Ile His
            340                 345                 350

Lys Leu Pro Ser Val Leu Val Leu Gln Leu Lys Arg Phe Glu His Leu
        355                 360                 365

Leu Asn Gly Ser Asn Arg Lys Leu Asp Asp Phe Ile Glu Phe Pro Thr
    370                 375                 380

Tyr Leu Asn Met Lys Asn Tyr Cys Ser Thr Lys Glu Lys Asp Lys His
385                 390                 395                 400

Ser Glu Asn Gly Lys Val Pro Asp Ile Ile Tyr Glu Leu Ile Gly Ile
                405                 410                 415

Val Ser His Lys Gly Thr Val Asn Glu Gly His Tyr Ile Ala Phe Cys
            420                 425                 430

Lys Ile Ser Gly Gly Gln Trp Phe Lys Phe Asn Asp Ser Met Val Ser
        435                 440                 445

Ser Ile Ser Gln Glu Glu Val Leu Lys Glu Gln Ala Tyr Leu Leu Phe
    450                 455                 460
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Tyr Thr Ile Arg Gln Val Asn
465                 470


<210> SEQ ID NO 10
<211> LENGTH: 1416
<212> TYPE: DNA
<213> ORGANISM: Saccharomyces cerevisiae

<400> SEQUENCE: 10

atgagcattt gtccacatat acagcaagta tttcagaatg aaaagtctaa agatggggtt     60

ctaaaaacgt gcaatgctgc caggtatata ttaaatcatt ccgtacccaa ggaaaaattc    120

ttaaacacca tgaaatgtgg tacatgccac gaaataaact ctggtgcaac tttcatgtgt    180

ctacaatgtg gattttgtgg atgttggaac cattcgcatt ttctctctca cagtaaacag    240

attggtcaca tatttggtat caactcaaat aatggccttt tattttgctt caaatgtgag    300

gactatatag ggaatatcga tctgattaac gatgctatcc tagcgaagta ttgggacgac    360

gtgtgcacaa agaccatggt tcctagcatg gaaagaagag atgggctttc tggcctgatc    420

aacatgggat ccacttgttt catgagtagt attctccaat gtctaatcca taacccttac    480

tttattaggc actcaatgag tcaaattcat tctaataatt gtaaagtgcg ttctccagat    540

aaatgttttt catgtgcact cgataaaatt gttcatgaac tttatggagc gctgaataca    600

aagcaagctt cttcgtcatc tacatctact aatcggcaaa ccggattcat atatctttta    660

acttgtgcct ggaaaatcaa tcaaaatcta gcagggtatt cacaacaaga tgctcatgaa    720

ttttggcagt ttataattaa ccaaatccac caaagctatg ttcttgattt gccaaatgcc    780

aaggaagtca gcagagcaaa taataagcag tgtgaatgca tagtgcatac tgtgtttgag    840

ggctccttgg aaagttctat tgtgtgtcca ggctgtcaaa ataattcaaa gacaaccatt    900

gatccattct tggatctttc tctggatatc aaggataaga aaaaacttta tgaatgtctt    960

gacagtttcc ataaaaaaga acagttgaag gatttcaact atcattgtgg ggagtgtaac   1020

agcactcaag atgcaataaa gcaactaggc atacacaaat taccatcggt tttggttttg   1080

caattgaaaa gattcgaaca cctacttaat ggaagtaaca gaaaactaga cgattttatt   1140

gaatttccaa cttatttaaa tatgaaaaat tactgttcaa cgaaggaaaa agataagcat   1200

tctgaaaatg gcaaggttcc agacattatt tacgaattaa tcggtattgt ttcccacaag   1260

gggacggtta atgagggaca ttatattgca ttttgtaaaa tttctggagg gcaatggttt   1320

aaattcaatg attccatggt ctcctctata tctcaagaag aggttttaaa ggaacaggca   1380

tatttattat tctacaccat tcgtcaagta aattga                             1416


<210> SEQ ID NO 11
<211> LENGTH: 1332
<212> TYPE: PRT
<213> ORGANISM: Saccharomyces cerevisiae

<400> SEQUENCE: 11

Met Thr Glu Arg Ile Pro Ile Lys Asn Tyr Gln Arg Thr Asn Ala Lys
1               5                   10                  15

Ala Leu Leu Lys Leu Thr Glu Lys Leu Phe Asn Lys Asn Phe Phe Asp
            20                  25                  30

Leu Tyr Leu Thr Ser Gln Gln Leu Val Val Leu Glu Tyr Leu Leu Ser
        35                  40                  45

Ile Ser Ser Glu Glu Asp Lys Leu Lys Ala Trp Asp Tyr Phe Leu Lys
    50                  55                  60
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Gly Asn Ile Ala Leu Asn Val Glu Lys Ser Phe Pro Leu Thr Gln Glu
65                  70                  75                  80

Glu Glu His His Gly Ala Val Ser Pro Ala Val Asp Thr Arg Ser Asp
                85                  90                  95

Asp Val Ser Ser Gln Thr Ile Lys Asp Asn Asn Asn Thr Asn Thr Asn
            100                 105                 110

Thr Ser Ile Ser Asn Glu Asn His Val Glu Asn Glu Ile Glu Asp Lys
        115                 120                 125

Gly Asp Asn Ala Ile Ala Asn Glu Asp Asn Phe Val Asn Asn Asp Glu
    130                 135                 140

Ser Asp Asn Val Glu Glu Asp Leu Phe Lys Leu Asp Leu Glu Asp Leu
145                 150                 155                 160

Lys Gln Gln Ile Ser Gly Thr Arg Phe Ile Gly Asn Leu Ser Leu Lys
                165                 170                 175

Ile Arg Tyr Val Leu Trp Gln Cys Ala Ile Asp Tyr Ile Tyr Cys Asp
            180                 185                 190

Arg Asn Glu Phe Gly Asp Glu Asn Asp Thr Glu Tyr Thr Leu Leu Asp
        195                 200                 205

Val Glu Glu Lys Glu Glu Glu Glu Ile Gly Lys Asn Glu Lys Pro Gln
    210                 215                 220

Asn Lys Glu Gly Ile Ser Lys Phe Ala Glu Asp Glu Asp Tyr Asp Asp
225                 230                 235                 240

Glu Asp Glu Asn Tyr Asp Glu Asp Ser Thr Asp Val Lys Asn Val Asp
                245                 250                 255

Asp Pro Pro Lys Asn Leu Asp Ser Ile Ser Ser Ser Asn Ile Glu Ile
            260                 265                 270

Asp Asp Glu Arg Arg Leu Val Leu Asn Ile Ser Ile Ser Lys Glu Thr
        275                 280                 285

Leu Ser Lys Leu Lys Thr Asn Asn Val Glu Glu Ile Met Gly Asn Trp
    290                 295                 300

Asn Lys Ile Tyr His Ser Phe Glu Tyr Asp Lys Glu Thr Met Ile Lys
305                 310                 315                 320

Arg Leu Lys Leu Glu Glu Ser Asp Lys Met Ile Glu Lys Gly Lys Lys
                325                 330                 335

Lys Arg Ser Arg Ser Asp Leu Glu Ala Ala Thr Asp Glu Gln Asp Arg
            340                 345                 350

Glu Asn Thr Asn Asp Glu Pro Asp Thr Asn Gln Lys Leu Pro Thr Pro
        355                 360                 365

Glu Gly Ser Thr Phe Ser Asp Thr Gly Asn Lys Arg Pro Lys Gln Ser
    370                 375                 380

Asn Leu Asp Leu Thr Val Asn Leu Gly Ile Glu Asn Leu Ser Leu Lys
385                 390                 395                 400

His Leu Leu Ser Ser Ile Gln Gln Lys Lys Ser Gln Leu Gly Ile Ser
                405                 410                 415

Asp Tyr Glu Leu Lys His Leu Ile Met Asp Val Arg Lys Asn Arg Ser
            420                 425                 430

Lys Trp Thr Ser Asp Glu Arg Ile Gly Gln Glu Glu Leu Tyr Glu Ala
        435                 440                 445

Cys Glu Lys Val Val Leu Glu Leu Arg Asn Tyr Thr Glu His Ser Thr
    450                 455                 460

Pro Phe Leu Asn Lys Val Ser Lys Arg Glu Ala Pro Asn Tyr His Gln
465                 470                 475                 480

Ile Ile Lys Lys Ser Met Asp Leu Asn Thr Val Leu Lys Lys Leu Lys
                485                 490                 495
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Ser Phe Gln Tyr Asp Ser Lys Gln Glu Phe Val Asp Asp Ile Met Leu
            500                 505                 510

Ile Trp Lys Asn Cys Leu Thr Tyr Asn Ser Asp Pro Ser His Phe Leu
        515                 520                 525

Arg Gly His Ala Ile Ala Met Gln Lys Lys Ser Leu Gln Leu Ile Arg
    530                 535                 540

Met Ile Pro Asn Ile Thr Ile Arg Asn Arg Ala Asp Leu Glu Lys Glu
545                 550                 555                 560

Ile Glu Asp Met Glu Lys Asp Lys Asp Tyr Glu Leu Asp Glu Glu Glu
                565                 570                 575

Glu Val Ala Gly Ser Gly Arg Lys Gly Leu Asn Met Gly Ala His Met
            580                 585                 590

Leu Ala Lys Glu Asn Gly Lys Val Ser Glu Lys Asp Ser Ser Lys Thr
        595                 600                 605

Val Lys Asp Glu Ala Pro Thr Asn Asp Asp Lys Leu Thr Ser Val Ile
    610                 615                 620

Pro Glu Gly Glu Lys Glu Lys Asp Lys Thr Ala Ser Ser Thr Val Thr
625                 630                 635                 640

Val His Glu Asn Val Asn Lys Asn Glu Ile Lys Glu Asn Gly Lys Asn
                645                 650                 655

Glu Glu Gln Asp Met Val Glu Glu Ser Ser Lys Thr Glu Asp Ser Ser
            660                 665                 670

Lys Asp Ala Asp Ala Ala Lys Lys Asp Thr Glu Asp Gly Leu Gln Asp
        675                 680                 685

Lys Thr Ala Glu Asn Lys Glu Ala Gly Glu Asn Asn Glu Glu Glu Glu
    690                 695                 700

Asp Asp Asp Asp Glu Asp Glu Asp Glu Asp Met Val Asp Ser Gln Ser
705                 710                 715                 720

Tyr Leu Leu Glu Lys Asp Asp Asp Arg Asp Asp Leu Glu Ile Ser Val
                725                 730                 735

Trp Lys Thr Val Thr Ala Lys Val Arg Ala Glu Ile Cys Leu Lys Arg
            740                 745                 750

Thr Glu Tyr Phe Lys Asn Gly Lys Leu Asn Ser Asp Ser Glu Ala Phe
        755                 760                 765

Leu Lys Asn Pro Gln Arg Met Lys Arg Phe Asp Gln Leu Phe Leu Glu
    770                 775                 780

Tyr Lys Glu Gln Lys Ala Leu Glu Ser Tyr Arg Gln Lys Ile Glu Gln
785                 790                 795                 800

Asn Ser Ile Met Lys Asn Gly Phe Gly Thr Val Leu Lys Gln Glu Asp
                805                 810                 815

Asp Asp Gln Leu Gln Phe His Asn Asp His Ser Leu Asn Gly Asn Glu
            820                 825                 830

Ala Phe Glu Lys Gln Pro Asn Asp Ile Glu Leu Asp Asp Thr Arg Phe
        835                 840                 845

Leu Gln Glu Tyr Asp Ile Ser Asn Ala Ile Pro Asp Ile Val Tyr Glu
    850                 855                 860

Gly Val Asn Thr Lys Thr Leu Asp Lys Met Glu Asp Ala Ser Val Asp
865                 870                 875                 880

Arg Met Leu Gln Asn Gly Ile Asn Lys Gln Ser Arg Phe Leu Ala Asn
                885                 890                 895

Lys Asp Leu Gly Leu Thr Pro Lys Met Asn Gln Asn Ile Thr Leu Ile
            900                 905                 910

Gln Gln Ile Arg His Ile Cys His Lys Ile Ser Leu Ile Arg Met Leu
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        915                 920                 925

Gln Ser Pro Leu Ser Ala Gln Asn Ser Arg Ser Asn Pro Asn Ala Phe
    930                 935                 940

Leu Asn Asn His Ile Tyr Asn Tyr Thr Ile Ile Asp Asp Ser Leu Asp
945                 950                 955                 960

Ile Asp Pro Val Ser Gln Leu Pro Thr His Asp Tyr Lys Asn Asn Arg
                965                 970                 975

Glu Leu Ile Trp Lys Phe Met His Lys Asn Ile Ser Lys Val Ala Met
            980                 985                 990

Ala Asn Gly Phe Glu Thr Ala His  Pro Ser Ala Ile Asn  Met Leu Thr
        995                 1000                1005

Glu Ile  Ala Gly Asp Tyr Leu  Ser Asn Leu Ile Lys  Thr Leu Lys
    1010                1015                1020

Leu His  His Glu Thr Asn Ser  Leu Asn Arg Gly Thr  Asn Val Glu
    1025                1030                1035

Met Leu  Gln Thr Thr Leu Leu  Glu Asn Gly Ile Asn  Arg Pro Asp
    1040                1045                1050

Asp Leu  Phe Ser Tyr Val Glu  Ser Glu Phe Gly Lys  Lys Thr Lys
    1055                1060                1065

Lys Leu  Gln Asp Ile Lys Gln  Lys Leu Glu Ser Phe  Leu Arg Ala
    1070                1075                1080

Leu Leu  Arg Pro Thr Leu Gln  Glu Leu Ser Glu Arg  Asn Phe Glu
    1085                1090                1095

Asp Glu  Ser Gln Ser Phe Phe  Thr Gly Asp Phe Ala  Ser Glu Leu
    1100                1105                1110

Thr Gly  Glu Asp Phe Phe Gly  Phe Arg Glu Leu Gly  Leu Glu Lys
    1115                1120                1125

Glu Phe  Gly Val Leu Ser Ser  Ser Val Pro Leu Gln  Leu Leu Thr
    1130                1135                1140

Thr Gln  Phe Gln Thr Val Asp  Gly Glu Thr Lys Val  Gln Ala Lys
    1145                1150                1155

Lys Ile  Gln Pro Glu Glu Ser  Asp Ser Ile Val Tyr  Lys Lys Ile
    1160                1165                1170

Thr Lys  Gly Met Leu Asp Ala  Gly Ser Phe Trp Asn  Thr Leu Leu
    1175                1180                1185

Pro Leu  Leu Gln Lys Asp Tyr  Glu Arg Ser Lys Ala  Tyr Ile Ala
    1190                1195                1200

Lys Gln  Ser Lys Ser Ser Ala  Asn Asp Lys Thr Ser  Met Thr Ser
    1205                1210                1215

Thr Glu  Asp Asn Ser Phe Ala  Leu Leu Glu Glu Asp  Gln Phe Val
    1220                1225                1230

Ser Lys  Lys Thr Ala Thr Lys  Ala Arg Leu Pro Pro  Thr Gly Lys
    1235                1240                1245

Ile Ser  Thr Thr Tyr Lys Lys  Lys Pro Ile Ala Ser  Ala Phe Ile
    1250                1255                1260

Leu Pro  Glu Glu Asp Leu Glu  Asn Asp Val Lys Ala  Asp Pro Thr
    1265                1270                1275

Thr Thr  Val Asn Ala Lys Val  Gly Ala Glu Asn Asp  Gly Asp Ser
    1280                1285                1290

Ser Leu  Phe Leu Arg Thr Pro  Gln Pro Leu Asp Pro  Leu Asp Met
    1295                1300                1305

Asp Asp  Ala Phe Asp Asp Thr  Asn Met Gly Ser Asn  Ser Ser Phe
    1310                1315                1320
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Ser Leu Ser Leu Pro Arg Leu Asn Gln
1325 1330

<210> SEQ ID NO 12
<211> LENGTH: 3999
<212> TYPE: DNA
<213> ORGANISM: Saccharomyces cerevisiae

<400> SEQUENCE: 12

atgactgaaa gaataccaat aaagaattat caaagaacaa atgccaaagc tttacttaaa 60

ttgactgaaa aacttttaa caagaacttt tttgatctct atttaacctc tcagcaattg 120

gtcgttcttg aatacctgct gtcgatttca agtgaagaag acaaactgaa agcatgggac 180

tatttcttaa agggaaacat agcattaaat gtcgaaaaat catttccatt aacccaagaa 240

gaagaacatc acggagcggt ctctcctgcc gttgacacac gatcagatga tgtatcatca 300

caaacaatta aggacaataa caatactaat accaacacca gtatcagcaa tgaaaatcat 360

gttgaaaatg aaattgaaga taaaggcgat aacgcaatag caaatgaaga taattttgtg 420

aataatgacg aaagtgataa tgttgaagaa gacttattca aattagatct agaggacttg 480

aagcagcaaa taagcggaac aaggtttatt ggaaacttat ccttgaaaat cagatacgtc 540

ttgtggcagt gcgccataga ttatatatac tgtgatcgta atgagtttgg tgatgaaaat 600

gatacagaat acaccctatt agatgttgaa gagaaggagg aagaggaaat tggtaaaaat 660

gagaagccac aaaacaaaga aggtatttcg aagttcgccg aggatgaaga ttacgacgat 720

gaagacgaga actatgatga agacagtaca gacgtaaaaa atgtcgatga tcctccaaaa 780

aatctcgatt ctatttcctc ttctaatatc gaaattgacg atgaacgacg cttggtgcta 840

aatatctcaa tatcaaaaga aacactgtca aagttaaaaa caaataatgt agaagaaatt 900

atgggaaatt ggaacaaaat ttaccacagt tttgaatacg ataaagaaac tatgataaag 960

cgattaaaac ttgaagaaag cgataaaatg atagagaaag gaaagaagaa acgaagtcga 1020

agtgatttag aagcagctac cgatgaacaa gatcgcgaaa atacaaatga tgagccagat 1080

actaatcaaa aattgcccac tcctgaaggt tcaacattca gcgatactgg gaacaagcgc 1140

cccaaacaaa gtaatttaga tttaacagtc aatctaggca tcgaaaattt atcattaaag 1200

caccttctat catctatcca gcaaaaaaaa tcccaattag gaatatcaga ttacgaatta 1260

aaacatctga ttatggatgt cagaaaaaat cggtcaaaat ggacatcgga tgaaagaatt 1320

gggcaagagg aattatacga agcctgtgaa aaggttgttt tggaacttag aaactacact 1380

gagcattcta caccatttct gaataaagtg agcaaaagag aagcccccaa ttatcatcaa 1440

atcatcaaaa agtccatgga cctgaatact gttttaaaaa aactgaaaag ctttcaatat 1500

gactccaaac aagaatttgt agacgatatt atgctaatat ggaaaaattg tttgacctat 1560

aattcagatc cttcacattt tttgagaggg catgctattg ctatgcagaa gaaatctctt 1620

cagttgattc gcatgattcc aaatatcaca atccgaaaca gggctgattt agaaaaggaa 1680

attgaagata tggaaaaaga caaagactac gaattagatg aggaagagga agttgctggt 1740

tctggaagaa aaggattgaa tatgggagct catatgttgg ccaaagagaa tggcaaggtg 1800

tcagaaaaag atagctctaa aaccgtcaag gatgaagcac caaccaatga tgacaaacta 1860

acttctgtca tccctgaggg ggaaaaagag aaagataaaa ctgcttcatc tactgtaacg 1920

gtacacgaaa atgtaaataa gaacgaaata aaagaaaatg ggaaaaatga agagcaagat 1980

atggttgagg aaagtagtaa gactgaggat tcatcaaaag atgctgatgc tgccaaaaag 2040

gatacggaag acggactaca agataaaact gcagaaaata aggaggctgg ggaaaataat 2100

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gaagaggaag aggatgatga tgacgaagat gaagacgaag acatggtcga ctcccaatct 2160

tatttacttg aaaaggatga cgatagagac gatttggaaa tatccgtgtg gaaaactgta 2220

actgccaaag ttcgtgcgga aatttgctta aaaagaactg aatattttaa aaatggaaaa 2280

ttaaatagtg attcagaggc gtttttgaaa aacccacaaa gaatgaaaag gttcgaccag 2340

ctttttcttg aatataaaga gcagaaagct ttagaatcat atcgtcaaaa aatagagcaa 2400

aattccatta tgaaaaatgg ctttggaaca gtactaaaac aggaagacga tgaccaattg 2460

cagtttcata atgatcactc tttaaatgga aatgaagctt ttgaaaagca acccaatgat 2520

attgagttag atgataccag attcctacag gaatatgata ttagtaacgc cattcctgac 2580

atagtatacg agggagtaaa tactaaaaca ttagacaaga tggaagacgc ttccgtggac 2640

cgcatgcttc aaaatggtat caacaaacaa agcagatttc tggctaacaa ggatttagga 2700

ctaacaccta aaatgaacca aaatatcaca ctgattcagc aaattaggca catatgccat 2760

aaaatatccc tgatcagaat gttacagagc cctttatcgg ctcaaaactc cagaagcaat 2820

cccaacgctt tccttaacaa ccacatttat aattacacta ttattgatga ctcactcgat 2880

attgatccgg tgtcacagct tccaacgcat gattacaaaa acaacaggga gctgatatgg 2940

aaattcatgc ataagaacat atctaaggtt gctatggcca atgggtttga aactgcccat 3000

ccatcagcaa taaacatgct tactgaaatc gccggggatt acctatctaa tctgataaag 3060

actttgaagc ttcatcatga aactaactcc ttaaatagag gaacaaatgt ggaaatgctg 3120

caaacaacac tgttggaaaa cggtatcaac aggccagacg atctattttc ctatgttgaa 3180

tctgaatttg gtaaaaaaac taagaaactt caggacatca aacagaaact agaaagcttt 3240

ttgagagcct tattaaggcc aactttgcag gagttgtccg agagaaactt tgaagacgag 3300

agccaaagct tttttacagg tgactttgcc agcgaattga ctggtgaaga cttctttggt 3360

tttagagagc ttggattaga aaaggagttt ggagttttga gttcatctgt tccattacag 3420

ttactgacta ctcagtttca aactgttgac ggggaaacca aagtgcaggc caaaaagatc 3480

caaccggaag aatcagacag cattgtgtat aagaaaatta caaaaggtat gctggatgct 3540

ggttcattct ggaatactct acttccccta ttacaaaaag attatgaacg ttccaaggcc 3600

tatatagcaa agcaaagcaa gtcatctgca aatgataaaa cctcaatgac ttccacagaa 3660

gacaattctt tcgctttact agaagaggat cagtttgtct caaagaaaac cgcaacgaag 3720

gcaagattac ctcctactgg taagataagt accacataca aaaagaaacc gatcgcaagc 3780

gcgtttatac ttccagaaga agacttggaa aacgacgtaa aagcggatcc aacaacaact 3840

gtaaacgcca aagtgggtgc agaaaatgat ggagattctt ccttattttt gcgaacgcct 3900

caacctttag atcctttgga tatggatgat gcttttgatg ataccaatat gggcagcaat 3960

agttcattta gcttgagcct tcctcgcctt aatcaataa 3999

<210> SEQ ID NO 13
<211> LENGTH: 602
<212> TYPE: PRT
<213> ORGANISM: Saccharomyces cerevisiae

<400> SEQUENCE: 13

Met Asp Glu Val Asp Asp Ile Leu Ile Asn Asn Gln Val Val Asp Asp
1 5 10 15

Glu Glu Asp Asp Glu Glu Met Leu Ser Gly Leu Glu Asn Asp Ser Lys
20 25 30

Gln Asp Leu Glu Gly Asn Asp Asp Gly Gly Glu Asp Glu Glu Asp Asp

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        35                  40                  45

Asp Asp Asp Asp Glu Asp Asp Asp Asp Asp Glu Asp Glu Arg Glu Asp
    50                  55                  60

Asp Asp Glu Gln Glu Asp Asp Asp Gly Glu Asp Asp Ala Ala Arg Met
65                  70                  75                  80

Asp Lys Thr Ala Thr Pro Thr Asn Glu His Gln His Asp Glu Gln Lys
                85                  90                  95

Ala Ala Ala Ala Gly Ala Gly Gly Ala Gly Asp Ser Gly Asp Ala Val
            100                 105                 110

Thr Lys Ile Gly Ser Glu Asp Val Lys Leu Ser Asp Val Asp Gly Gly
        115                 120                 125

Val Gly Ser Arg Glu Ala Ser Ser Ser Thr His Glu Ala Ser Ala Asn
    130                 135                 140

Gly Glu Val Tyr Glu Tyr Tyr Lys His Met Leu Asn Ala Ala Gln Ile
145                 150                 155                 160

Ala Asp Ser Tyr Asn Ile Tyr Pro Thr Ala Ala Ile Pro Ile Gln Thr
                165                 170                 175

His Val Asn Ala Leu Ala Val Ser Arg Gly Leu Lys Tyr Leu Phe Leu
            180                 185                 190

Gly Gly Ser Asp Gly Tyr Ile Arg Lys Tyr Asp Leu Leu Asn Thr Leu
        195                 200                 205

Glu Gly Lys Leu Ser Leu Thr Ile Leu Gln Lys His Ser Leu Ala Glu
    210                 215                 220

Ser Ile Gln Asn Ala Gly Ile Leu Gln Ser Tyr Trp Glu Asn Glu Ile
225                 230                 235                 240

Pro Gln Lys Lys Ser Glu Met Lys Leu Ser Ala Asn Lys Thr Asp Tyr
                245                 250                 255

Glu Pro Lys Val Ser Pro Val His Ser Leu Glu Val Gln Ser Glu Cys
            260                 265                 270

Leu Phe Ile Leu Ser Gly Leu Gln Asn Gly Gly Ile Thr Met Gln Gly
        275                 280                 285

Val Arg Tyr Met Glu Gly Ser Ile Ala His Tyr Phe Lys Gly Arg Asn
    290                 295                 300

Gly His Thr Gln Ile Val Asn Ile Leu Arg Leu Asn Gly Gln Glu Asp
305                 310                 315                 320

Arg Phe Leu Ser Gly Ser Trp Asp Lys Arg Leu Leu Glu Trp Asp Leu
                325                 330                 335

Gln Thr Gly Asp Ile Val Asn Glu Phe Lys Lys Ser Arg Ser Glu Leu
            340                 345                 350

Ser Ser Leu Glu Met Arg Pro Leu Tyr Ser Ser Val Asp Val Ser Gly
        355                 360                 365

Asn Val Asn Ser Gly Lys Glu Asn Glu Asn Ala Asp Asp Asp Met Asp
    370                 375                 380

Ser Leu Phe Gly Asp Glu Asp Glu Asp Glu Lys Gln Asp Ala Gly Asn
385                 390                 395                 400

Glu Pro Val Glu Thr Gly Asp Gly Ser Asn Gly Glu Glu Asn Lys Glu
                405                 410                 415

Gln Ile Ser Glu Glu Ser Leu Asn Ile Val Tyr Asp Glu Ser Val Phe
            420                 425                 430

Met Thr Ser Gly Leu Asn Gly Ser Val His Ile Trp Asp Arg Arg Met
        435                 440                 445

Thr Gln Ser Pro Ala Leu Ser Leu Glu Arg Gly Ala Gly Val Pro Pro
    450                 455                 460
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Trp Cys Leu Ser Ala Cys Trp Gly Val Asp Gly Asp His Val Tyr Ala
465                 470                 475                 480

Gly Arg Arg Asn Ala Cys Val Glu Gln Phe Asp Leu Lys Met Pro Ser
                485                 490                 495

Lys Pro Ile His Asn Leu Lys Leu Pro Ser Ile Ser Gly Pro Val Ser
            500                 505                 510

Cys Val Lys Ala Met Pro Asn Asn Lys His Leu Leu Cys Ala Ser Arg
        515                 520                 525

Asp Asn Ile Arg Leu Tyr Asn Val Glu Ile Ala Val Asp Ala Ser Asn
    530                 535                 540

Ser Thr Thr Lys Ser Ser Lys Val Pro Phe Leu Ile Val Pro Gly His
545                 550                 555                 560

His Gly Gly Ile Ile Ser Asn Leu Tyr Leu Asp Pro Thr Ser Arg Phe
                565                 570                 575

Ile Ile Ser Thr Ser Gly Asn Arg Gly Trp Gln Gly Asn Ser Thr Asp
            580                 585                 590

Thr Thr Leu Ile Tyr Asp Ile Asp Leu Glu
        595                 600


<210> SEQ ID NO 14
<211> LENGTH: 1809
<212> TYPE: DNA
<213> ORGANISM: Saccharomyces cerevisiae

<400> SEQUENCE: 14

atggacgagg ttgacgatat tctaattaac aaccaggtgg tggatgacga ggaggatgac     60

gaagagatgc tgagtgggct ggaaaacgac tcaaagcagg acctcgaggg gaatgatgac    120

ggtggtgaag atgaagagga tgacgatgat gatgatgagg acgatgatga tgacgaggac    180

gaacgagagg acgacgatga acaggaggac gacgatggtg aggacgacgc cgcaagaatg    240

gataagactg ctacaccgac gaatgagcac cagcatgatg agcaaaaggc tgctgctgct    300

ggtgctggcg gtgcaggcga tagtggcgat gctgttacta agattggatc cgaggatgtg    360

aaattgagcg atgttgatgg aggagtgggg tccagggaag catcttcctc tacacacgaa    420

gcctctgcta atggagaggt ttatgagtac tataagcaca tgttgaatgc cgcacagatt    480

gcggattcgt acaatatcta ccccacggca gccataccca tccagacgca cgtcaatgcg    540

ttggccgtgt ccaggggtct caagtacctg tttttgggcg gtagcgatgg atacataagg    600

aagtacgact tgctgaacac gcttgagggg aaactttctc taactatcct gcagaagcat    660

tcgttggctg agtctattca gaacgcgggt atcttgcagt cgtactggga aaatgagatc    720

ccgcagaaaa aatcagaaat gaaactctcc gctaataaga cagattacga gcccaaagtt    780

agccccgttc attctttgga agtccaaagc gaatgcctct ttatactgag cgggctacag    840

aatggtggga ttaccatgca gggcgttcgc tacatggagg ggagcattgc gcactatttt    900

aagggcagga atggacatac ccaaatcgtt aacatactga gattaaacgg tcaagaggac    960

aggtttttga gtggttcctg ggataagcgt cttttggaat gggatttgca gacgggtgac   1020

atagttaatg agtttaaaaa atcaaggtct gaattgtcat ctttggaaat gcggccgctg   1080

tactcgtccg tggatgtgtc cggtaacgtc aacagtggta aagagaatga aaatgcagat   1140

gacgatatgg attctctgtt tggtgatgaa gacgaagacg aaaagcaaga tgctggcaac   1200

gaacccgtcg agacgggggga tggttctaat ggtgaagaga acaaagaaca gatatctgaa   1260

gaatctttga acatagtcta tgatgaatcc gtttttatga cctcagggtt gaacggttcc   1320

gtgcatattt gggaccgacg catgacgcag tcgccagcat tgtctctgga gagaggtgca   1380
```

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ggcgtcccac cgtggtgttt gtccgcatgt tggggtgtag atggtgatca tgtgtatgca   1440

gggagaagga atgcctgtgt ggagcagttt gacttgaaga tgccctcgaa acctatccat   1500

aatttgaaac tgccttctat ttcagggcct gtctcttgtg ttaaagccat gcctaataac   1560

aagcatttac tatgtgcatc gcgggataat atcagattgt acaacgttga aattgcagta   1620

gatgcttcga attcgactac aaagagttct aaagtgccgt tcctcatcgt gccgggccat   1680

cacggtggta ttatatcaaa cttatacctc gaccccactt caagatttat aataagcaca   1740

agtggcaaca gaggctggca ggggaattct acggacacga cccttattta cgatatagac   1800

ttagaatag                                                           1809
```

<210> SEQ ID NO 15
<211> LENGTH: 633
<212> TYPE: PRT
<213> ORGANISM: Saccharomyces cerevisiae

<400> SEQUENCE: 15

```
Met Ser Ser Asn Asn Asn Thr Asn Thr Ala Pro Ala Asn Ala Asn Ser
1               5                   10                  15

Ser His His His His His His His His His His His His Gly His
            20                  25                  30

Gly Gly Ser Asn Ser Thr Leu Asn Asn Pro Lys Ser Ser Leu Ala Asp
        35                  40                  45

Gly Ala His Ile Gly Asn Tyr Gln Ile Val Lys Thr Leu Gly Glu Gly
    50                  55                  60

Ser Phe Gly Lys Val Lys Leu Ala Tyr His Thr Thr Thr Gly Gln Lys
65                  70                  75                  80

Val Ala Leu Lys Ile Ile Asn Lys Lys Val Leu Ala Lys Ser Asp Met
                85                  90                  95

Gln Gly Arg Ile Glu Arg Glu Ile Ser Tyr Leu Arg Leu Leu Arg His
            100                 105                 110

Pro His Ile Ile Lys Leu Tyr Asp Val Ile Lys Ser Lys Asp Glu Ile
        115                 120                 125

Ile Met Val Ile Glu Tyr Ala Gly Asn Glu Leu Phe Asp Tyr Ile Val
    130                 135                 140

Gln Arg Asp Lys Met Ser Glu Gln Glu Ala Arg Arg Phe Phe Gln Gln
145                 150                 155                 160

Ile Ile Ser Ala Val Glu Tyr Cys His Arg His Lys Ile Val His Arg
                165                 170                 175

Asp Leu Lys Pro Glu Asn Leu Leu Leu Asp Glu His Leu Asn Val Lys
            180                 185                 190

Ile Ala Asp Phe Gly Leu Ser Asn Ile Met Thr Asp Gly Asn Phe Leu
        195                 200                 205

Lys Thr Ser Cys Gly Ser Pro Asn Tyr Ala Ala Pro Glu Val Ile Ser
    210                 215                 220

Gly Lys Leu Tyr Ala Gly Pro Glu Val Asp Val Trp Ser Cys Gly Val
225                 230                 235                 240

Ile Leu Tyr Val Met Leu Cys Arg Arg Leu Pro Phe Asp Asp Glu Ser
                245                 250                 255

Ile Pro Val Leu Phe Lys Asn Ile Ser Asn Gly Val Tyr Thr Leu Pro
            260                 265                 270

Lys Phe Leu Ser Pro Gly Ala Ala Gly Leu Ile Lys Arg Met Leu Ile
        275                 280                 285

Val Asn Pro Leu Asn Arg Ile Ser Ile His Glu Ile Met Gln Asp Asp
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    290                 295                 300

Trp Phe Lys Val Asp Leu Pro Glu Tyr Leu Leu Pro Pro Asp Leu Lys
305                 310                 315                 320

Pro His Pro Glu Glu Glu Asn Glu Asn Asn Asp Ser Lys Lys Asp Gly
                325                 330                 335

Ser Ser Pro Asp Asn Asp Glu Ile Asp Asp Asn Leu Val Asn Ile Leu
            340                 345                 350

Ser Ser Thr Met Gly Tyr Glu Lys Asp Glu Ile Tyr Glu Ser Leu Glu
        355                 360                 365

Ser Ser Glu Asp Thr Pro Ala Phe Asn Glu Ile Arg Asp Ala Tyr Met
    370                 375                 380

Leu Ile Lys Glu Asn Lys Ser Leu Ile Lys Asp Met Lys Ala Asn Lys
385                 390                 395                 400

Ser Val Ser Asp Glu Leu Asp Thr Phe Leu Ser Gln Ser Pro Pro Thr
                405                 410                 415

Phe Gln Gln Gln Ser Lys Ser His Gln Lys Ser Gln Val Asp His Glu
            420                 425                 430

Thr Ala Lys Gln His Ala Arg Arg Met Ala Ser Ala Ile Thr Gln Gln
        435                 440                 445

Arg Thr Tyr His Gln Ser Pro Phe Met Asp Gln Tyr Lys Glu Glu Asp
    450                 455                 460

Ser Thr Val Ser Ile Leu Pro Thr Ser Leu Pro Gln Ile His Arg Ala
465                 470                 475                 480

Asn Met Leu Ala Gln Gly Ser Pro Ala Ala Ser Lys Ile Ser Pro Leu
                485                 490                 495

Val Thr Lys Lys Ser Lys Thr Arg Trp His Phe Gly Ile Arg Ser Arg
            500                 505                 510

Ser Tyr Pro Leu Asp Val Met Gly Glu Ile Tyr Ile Ala Leu Lys Asn
        515                 520                 525

Leu Gly Ala Glu Trp Ala Lys Pro Ser Glu Glu Asp Leu Trp Thr Ile
    530                 535                 540

Lys Leu Arg Trp Lys Tyr Asp Ile Gly Asn Lys Thr Asn Thr Asn Glu
545                 550                 555                 560

Lys Ile Pro Asp Leu Met Lys Met Val Ile Gln Leu Phe Gln Ile Glu
                565                 570                 575

Thr Asn Asn Tyr Leu Val Asp Phe Lys Phe Asp Gly Trp Glu Ser Ser
            580                 585                 590

Tyr Gly Asp Asp Thr Thr Val Ser Asn Ile Ser Glu Asp Glu Met Ser
        595                 600                 605

Thr Phe Ser Ala Tyr Pro Phe Leu His Leu Thr Thr Lys Leu Ile Met
    610                 615                 620

Glu Leu Ala Val Asn Ser Gln Ser Asn
625                 630


<210> SEQ ID NO 16
<211> LENGTH: 1902
<212> TYPE: DNA
<213> ORGANISM: Saccharomyces cerevisiae

<400> SEQUENCE: 16

atgagcagta acaacaacac aaacacagca cctgccaatg caaattctag ccaccaccac     60

caccatcacc accatcacca ccaccatcac ggtcatggcg gaagcaactc gacgctaaac    120

aatcccaagt cgtccttagc ggatggtgca catatcggga actaccaaat cgtcaaaacg    180

ctgggagagg ggtcctttgg taaagttaaa ttggcatatc ataccactac gggccaaaaa    240
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gttgctctaa aaatcattaa taagaaggtt ttggcaaaga gtgatatgca gggcagaatt 300

gaaagagaaa tatcttatct gagactctta agacaccccc acatcatcaa actgtatgat 360

gttatcaaat ccaaagatga aatcattatg gttatagagt acgccgggaa cgaattgttt 420

gactatattg ttcagagaga caaaatgagc gagcaagagg caagaagatt tttccagcag 480

atcatcagtg ccgtcgagta ctgccatagg cacaaaattg tccatagaga tctgaagcct 540

gaaaacttac tactagatga gcatctgaat gtaaagattg ccgattttgg tttgtcaaac 600

atcatgactg atggtaattt cttaaagact tcttgtggtt ctcccaatta tgcggctcct 660

gaagttatca gcggtaagct gtacgcaggc ccagaagtgg acgtgtggtc atgtggggtt 720

atcctttatg ttatgctttg tcgtcgtcta ccgtttgacg atgaaagcat cccagtgctt 780

ttcaagaata tcagcaacgg tgtttacacc ttgcctaaat ttttatctcc tggagctgct 840

gggctaatca aaagaatgtt aatcgttaat ccattgaaca gaataagcat tcatgaaatt 900

atgcaagacg attggttcaa agttgacctg ccagaatatc tacttccacc agatttgaaa 960

ccacacccag aagaagagaa tgaaaataat gactcaaaaa aggatggcag cagcccagat 1020

aacgatgaaa ttgatgacaa ccttgtcaat attttatcat cgaccatggg ttacgaaaaa 1080

gacgagattt atgagtcctt agaatcatca gaagacactc ctgcattcaa cgaaattagg 1140

gacgcgtaca tgttgattaa ggagaataaa tctttgatca aggatatgaa ggcaaacaaa 1200

agcgtcagtg atgaactgga tacctttctg tcccagtcac ctccaacttt tcaacaacaa 1260

agcaaatccc atcaaaagag tcaagtagat catgaaactg ccaagcaaca cgcaagaagg 1320

atggcaagtg ctatcactca acaaaggaca tatcaccaat cacccttcat ggatcagtat 1380

aaagaagaag actctacagt ttccattttg cctacatctt tacctcagat ccacagagct 1440

aatatgttag cacaaggttc gccagctgcc tctaaaatat ctcctcttgt aacgaaaaaa 1500

tctaaaacga gatggcattt tggtatacga tctcgctcat atccattaga cgttatgggt 1560

gaaatttata ttgccttgaa gaatttgggt gccgaatggg ccaagccatc tgaagaggat 1620

ttatggacta tcaaattaag gtggaaatat gatattggaa acaagacaaa cactaatgaa 1680

aaaatacctg atttaatgaa aatggtaatt caattatttc aaattgaaac caataattat 1740

ttggtggatt tcaaatttga cggctgggaa agtagttatg gagatgatac tactgtttct 1800

aatatttctg aagatgaaat gagtactttt tcagcctacc catttttaca tttaacaaca 1860

aaactaatta tggaattagc cgttaacagt caaagcaatt ga 1902

<210> SEQ ID NO 17
<211> LENGTH: 713
<212> TYPE: PRT
<213> ORGANISM: Saccharomyces cerevisiae

<400> SEQUENCE: 17

Met Ser Pro Ser Ala Val Gln Ser Ser Lys Leu Glu Glu Gln Ser Ser
1 5 10 15

Glu Ile Asp Lys Leu Lys Ala Lys Met Ser Gln Ser Ala Ala Thr Ala
20 25 30

Gln Arg Lys Lys Glu His Glu Tyr Glu His Leu Thr Ser Val Lys Ile
35 40 45

Val Pro Gln Arg Pro Ile Ser Asp Arg Leu Gln Pro Ala Ile Ala Thr
50 55 60

His Tyr Ser Pro His Leu Asp Gly Leu Gln Asp Tyr Gln Arg Leu His
65 70 75 80

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Lys Glu Ser Ile Glu Asp Pro Ala Lys Phe Phe Gly Ser Lys Ala Thr
                85                  90                  95

Gln Phe Leu Asn Trp Ser Lys Pro Phe Asp Lys Val Phe Ile Pro Asp
            100                 105                 110

Pro Lys Thr Gly Arg Pro Ser Phe Gln Asn Asn Ala Trp Phe Leu Asn
        115                 120                 125

Gly Gln Leu Asn Ala Cys Tyr Asn Cys Val Asp Arg His Ala Leu Lys
    130                 135                 140

Thr Pro Asn Lys Lys Ala Ile Ile Phe Glu Gly Asp Glu Pro Gly Gln
145                 150                 155                 160

Gly Tyr Ser Ile Thr Tyr Lys Glu Leu Leu Glu Glu Val Cys Gln Val
                165                 170                 175

Ala Gln Val Leu Thr Tyr Ser Met Gly Val Arg Lys Gly Asp Thr Val
            180                 185                 190

Ala Val Tyr Met Pro Met Val Pro Glu Ala Ile Ile Thr Leu Leu Ala
        195                 200                 205

Ile Ser Arg Ile Gly Ala Ile His Ser Val Val Phe Ala Gly Phe Ser
    210                 215                 220

Ser Asn Ser Leu Arg Asp Arg Ile Asn Asp Gly Asp Ser Lys Val Val
225                 230                 235                 240

Ile Thr Thr Asp Glu Ser Asn Arg Gly Gly Lys Val Ile Glu Thr Lys
                245                 250                 255

Arg Ile Val Asp Asp Ala Leu Arg Glu Thr Pro Gly Val Arg His Val
            260                 265                 270

Leu Val Tyr Arg Lys Thr Asn Asn Pro Ser Val Ala Phe His Ala Pro
        275                 280                 285

Arg Asp Leu Asp Trp Ala Thr Glu Lys Lys Lys Tyr Lys Thr Tyr Tyr
    290                 295                 300

Pro Cys Thr Pro Val Asp Ser Glu Asp Pro Leu Phe Leu Leu Tyr Thr
305                 310                 315                 320

Ser Gly Ser Thr Gly Ala Pro Lys Gly Val Gln His Ser Thr Ala Gly
                325                 330                 335

Tyr Leu Leu Gly Ala Leu Leu Thr Met Arg Tyr Thr Phe Asp Thr His
            340                 345                 350

Gln Glu Asp Val Phe Phe Thr Ala Gly Asp Ile Gly Trp Ile Thr Gly
        355                 360                 365

His Thr Tyr Val Val Tyr Gly Pro Leu Leu Tyr Gly Cys Ala Thr Leu
    370                 375                 380

Val Phe Glu Gly Thr Pro Ala Tyr Pro Asn Tyr Ser Arg Tyr Trp Asp
385                 390                 395                 400

Ile Ile Asp Glu His Lys Val Thr Gln Phe Tyr Val Ala Pro Thr Ala
                405                 410                 415

Leu Arg Leu Leu Lys Arg Ala Gly Asp Ser Tyr Ile Glu Asn His Ser
            420                 425                 430

Leu Lys Ser Leu Arg Cys Leu Gly Ser Val Gly Glu Pro Ile Ala Ala
        435                 440                 445

Glu Val Trp Glu Trp Tyr Ser Glu Lys Ile Gly Lys Asn Glu Ile Pro
    450                 455                 460

Ile Val Asp Thr Tyr Trp Gln Thr Glu Ser Gly Ser His Leu Val Thr
465                 470                 475                 480

Pro Leu Ala Gly Gly Val Thr Pro Met Lys Pro Gly Ser Ala Ser Phe
                485                 490                 495

Pro Phe Phe Gly Ile Asp Ala Val Val Leu Asp Pro Asn Thr Gly Glu
            500                 505                 510
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```
Glu Leu Asn Thr Ser His Ala Glu Gly Val Leu Ala Val Lys Ala Ala
        515                 520                 525

Trp Pro Ser Phe Ala Arg Thr Ile Trp Lys Asn His Asp Arg Tyr Leu
    530                 535                 540

Asp Thr Tyr Leu Asn Pro Tyr Pro Gly Tyr Tyr Phe Thr Gly Asp Gly
545                 550                 555                 560

Ala Ala Lys Asp Lys Asp Gly Tyr Ile Trp Ile Leu Gly Arg Val Asp
                565                 570                 575

Asp Val Val Asn Val Ser Gly His Arg Leu Ser Thr Ala Glu Ile Glu
            580                 585                 590

Ala Ala Ile Ile Glu Asp Pro Ile Val Ala Glu Cys Ala Val Val Gly
        595                 600                 605

Phe Asn Asp Asp Leu Thr Gly Gln Ala Val Ala Ala Phe Val Val Leu
    610                 615                 620

Lys Asn Lys Ser Ser Trp Ser Thr Ala Thr Asp Asp Glu Leu Gln Asp
625                 630                 635                 640

Ile Lys Lys His Leu Val Phe Thr Val Arg Lys Asp Ile Gly Pro Phe
                645                 650                 655

Ala Ala Pro Lys Leu Ile Ile Leu Val Asp Asp Leu Pro Lys Thr Arg
            660                 665                 670

Ser Gly Lys Ile Met Arg Arg Ile Leu Arg Lys Ile Leu Ala Gly Glu
        675                 680                 685

Ser Asp Gln Leu Gly Asp Val Ser Thr Leu Ser Asn Pro Gly Ile Val
    690                 695                 700

Arg His Leu Ile Asp Ser Val Lys Leu
705                 710


<210> SEQ ID NO 18
<211> LENGTH: 2142
<212> TYPE: DNA
<213> ORGANISM: Saccharomyces cerevisiae

<400> SEQUENCE: 18

atgtcgccct ctgccgtaca atcatcaaaa ctagaagaac agtcaagtga aattgacaag     60

ttgaaagcaa aaatgtccca gtctgccgcc actgcgcagc agaagaagga acatgagtat    120

gaacatttga cttcggtcaa gatcgtgcca caacggccca tctcagatag actgcagccc    180

gcaattgcta cccactattc tccacacttg gacgggttgc aggactatca gcgcttgcac    240

aaggagtcta ttgaagaccc tgctaagttc ttcggttcta aagctaccca atttttaaac    300

tggtctaagc cattcgataa ggtgttcatc ccagacccta aaacgggcag gccctccttc    360

cagaacaatg catggttcct caacggccaa ttaaacgcct gttacaactg tgttgacaga    420

catgccttga agactcctaa caagaaagcc attattttcg aaggtgacga gcctggccaa    480

ggctattcca ttacctacaa ggaactactt gaagaagttt gtcaagtggc acaagtgctg    540

acttactcta tgggcgttcg caagggcgat actgttgccg tgtacatgcc tatggtccca    600

gaagcaatca taaccttgtt ggccatttcc cgtatcggtg ccattcactc cgtagtcttt    660

gccgggtttt cttccaactc cttgagagat cgtatcaacg atggggactc taaagttgtc    720

atcactacag atgaatccaa cagaggtggt aaagtcattg agactaaaag aattgttgat    780

gacgcgctaa gagagacccc aggcgtgaga cacgtcttgg tttatagaaa gaccaacaat    840

ccatctgttg ctttccatgc ccccagagat ttggattggg caacagaaaa gaagaaatac    900

aagacctact atccatgcac acccgttgat tctgaggatc cattattctt gttgtatacg    960
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tctggttcta ctggtgcccc caagggtgtt caacattcta ccgcaggtta cttgctggga   1020

gctttgttga ccatgcgcta cacttttgac actcaccaag aagacgtttt cttcacagct   1080

ggagacattg gctggattac aggccacact tatgtggttt atggtccctt actatatggt   1140

tgtgccactt tggtctttga agggactcct gcgtacccaa attactcccg ttattgggat   1200

attattgatg aacacaaagt cacccaattt tatgttgcgc caactgcttt gcgtttgttg   1260

aaaagagctg gtgattccta catcgaaaat cattccttaa aatctttgcg ttgcttgggt   1320

tcggtcggtg agccaattgc tgctgaagtt tgggagtggt actctgaaaa aataggtaaa   1380

aatgaaatcc ccattgtaga cacctactgg caaacagaat ctggttcgca tctggtcacc   1440

ccgctggctg gtggtgttac accaatgaaa ccgggttctg cctcattccc cttcttcggt   1500

attgatgcag ttgttcttga ccctaacact ggtgaagaac ttaacaccag ccacgcagag   1560

ggtgtccttg ccgtcaaagc tgcatggcca tcatttgcaa gaactatttg gaaaaatcat   1620

gataggtatc tagacactta tttgaaccct taccctggct actatttcac tggtgatggt   1680

gctgcaaagg ataaggatgg ttatatctgg attttgggtc gtgtagacga tgtggtgaac   1740

gtctctggtc accgtctgtc taccgctgaa attgaggctg ctattatcga agatccaatt   1800

gtggccgagt gtgctgttgt cggattcaac gatgacttga ctggtcaagc agttgctgca   1860

tttgtggtgt tgaaaaacaa atctagttgg tccaccgcaa cagatgatga attacaagat   1920

atcaagaagc atttggtctt tactgttaga aaagacatcg ggccatttgc cgcaccaaaa   1980

ttgatcattt tagtggatga cttgcccaag acaagatccg gcaaaattat gagacgtatt   2040

ttaagaaaaa tcctagcagg agaaagtgac caactaggcg acgtttctac attgtcaaac   2100

cctggcattg ttagacatct aattgattcg gtcaagttgt aa                      2142
```

<210> SEQ ID NO 19
<211> LENGTH: 1119
<212> TYPE: PRT
<213> ORGANISM: Saccharomyces cerevisiae

<400> SEQUENCE: 19

```
Met Thr Glu Arg Ile Pro Ile Lys Asn Tyr Gln Arg Thr Asn Ala Lys
1               5                   10                  15

Ala Leu Leu Lys Leu Thr Glu Lys Leu Phe Asn Lys Asn Phe Phe Asp
            20                  25                  30

Leu Tyr Leu Thr Ser Gln Gln Leu Val Val Leu Glu Tyr Leu Leu Ser
        35                  40                  45

Ile Ser Ser Glu Glu Asp Lys Leu Lys Ala Trp Asp Tyr Phe Leu Lys
    50                  55                  60

Gly Asn Ile Ala Leu Asn Val Glu Lys Ser Phe Pro Leu Thr Gln Glu
65                  70                  75                  80

Glu Glu His His Gly Ala Val Ser Pro Ala Val Asp Thr Arg Ser Asp
                85                  90                  95

Asp Val Ser Ser Gln Thr Ile Lys Asp Asn Asn Asn Thr Asn Thr Asn
            100                 105                 110

Thr Ser Ile Ser Asn Glu Asn His Val Glu Asn Glu Ile Glu Asp Lys
        115                 120                 125

Gly Asp Asn Ala Ile Ala Asn Glu Asp Asn Phe Val Asn Asn Asp Glu
    130                 135                 140

Ser Asp Asn Val Glu Glu Asp Leu Phe Lys Leu Asp Leu Glu Asp Leu
145                 150                 155                 160

Lys Gln Gln Ile Ser Gly Thr Arg Phe Ile Gly Asn Leu Ser Leu Lys
                165                 170                 175
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```
Ile Arg Tyr Val Leu Trp Gln Cys Ala Ile Asp Tyr Ile Tyr Cys Asp
            180                 185                 190

Arg Asn Glu Phe Gly Asp Glu Asn Asp Thr Glu Tyr Thr Leu Leu Asp
        195                 200                 205

Val Glu Glu Lys Glu Glu Glu Glu Ile Gly Lys Asn Glu Lys Pro Gln
    210                 215                 220

Asn Lys Glu Gly Ile Ser Lys Phe Ala Glu Asp Glu Asp Tyr Asp Asp
225                 230                 235                 240

Glu Asp Glu Asn Tyr Asp Glu Asp Ser Thr Asp Val Lys Asn Val Asp
                245                 250                 255

Asp Pro Pro Lys Asn Leu Asp Ser Ile Ser Ser Ser Asn Ile Glu Ile
            260                 265                 270

Asp Asp Glu Arg Arg Leu Val Leu Asn Ile Ser Ile Ser Lys Glu Thr
        275                 280                 285

Leu Ser Lys Leu Lys Thr Asn Asn Val Glu Glu Ile Met Gly Asn Trp
    290                 295                 300

Asn Lys Ile Tyr His Ser Phe Glu Tyr Asp Lys Glu Thr Met Ile Lys
305                 310                 315                 320

Arg Leu Lys Leu Glu Glu Ser Asp Lys Met Ile Glu Lys Gly Lys Lys
                325                 330                 335

Lys Arg Ser Arg Ser Asp Leu Glu Ala Ala Thr Asp Glu Gln Asp Arg
            340                 345                 350

Glu Asn Thr Asn Asp Glu Pro Asp Thr Asn Gln Lys Leu Pro Thr Pro
        355                 360                 365

Glu Gly Ser Thr Phe Ser Asp Thr Gly Asn Lys Arg Pro Lys Gln Ser
    370                 375                 380

Asn Leu Asp Leu Thr Val Asn Leu Gly Ile Glu Asn Leu Ser Leu Lys
385                 390                 395                 400

His Leu Leu Ser Ser Ile Gln Gln Lys Lys Ser Gln Leu Gly Ile Ser
                405                 410                 415

Asp Tyr Glu Leu Lys His Leu Ile Met Asp Val Arg Lys Asn Arg Ser
            420                 425                 430

Lys Trp Thr Ser Asp Glu Arg Ile Gly Gln Glu Glu Leu Tyr Glu Ala
        435                 440                 445

Cys Glu Lys Val Val Leu Glu Leu Arg Asn Tyr Thr Glu His Ser Thr
    450                 455                 460

Pro Phe Leu Asn Lys Val Ser Lys Arg Glu Ala Pro Asn Tyr His Gln
465                 470                 475                 480

Ile Ile Lys Lys Ser Met Asp Leu Asn Thr Val Leu Lys Lys Leu Lys
                485                 490                 495

Ser Phe Gln Tyr Asp Ser Lys Gln Glu Phe Val Asp Asp Ile Met Leu
            500                 505                 510

Ile Trp Lys Asn Cys Leu Thr Tyr Asn Ser Asp Pro Ser His Phe Leu
        515                 520                 525

Arg Gly His Ala Ile Ala Met Gln Lys Lys Ser Leu Gln Leu Ile Arg
    530                 535                 540

Met Ile Pro Asn Ile Thr Ile Arg Asn Arg Ala Asp Leu Glu Lys Glu
545                 550                 555                 560

Ile Glu Asp Met Glu Lys Asp Lys Asp Tyr Glu Leu Asp Glu Glu Glu
                565                 570                 575

Glu Val Ala Gly Ser Gly Arg Lys Gly Leu Asn Met Gly Ala His Met
            580                 585                 590

Leu Ala Lys Glu Asn Gly Lys Val Ser Glu Lys Asp Ser Ser Lys Thr
```

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        595                 600                 605

Val Lys Asp Glu Ala Pro Thr Asn Asp Asp Lys Leu Thr Ser Val Ile
    610                 615                 620

Pro Glu Gly Glu Lys Glu Lys Asp Lys Thr Ala Ser Ser Thr Val Thr
625                 630                 635                 640

Val His Glu Asn Val Asn Lys Asn Glu Ile Lys Glu Asn Gly Lys Asn
                645                 650                 655

Glu Glu Gln Asp Met Val Glu Glu Ser Ser Lys Thr Glu Asp Ser Ser
            660                 665                 670

Lys Asp Ala Asp Ala Ala Lys Lys Asp Thr Glu Asp Gly Leu Gln Asp
        675                 680                 685

Lys Thr Ala Glu Asn Lys Glu Ala Gly Glu Asn Asn Glu Glu Glu Glu
    690                 695                 700

Asp Asp Asp Asp Glu Asp Glu Asp Glu Asp Met Val Asp Ser Gln Ser
705                 710                 715                 720

Tyr Leu Leu Glu Lys Asp Asp Asp Arg Asp Asp Leu Glu Ile Ser Val
                725                 730                 735

Trp Lys Thr Val Thr Ala Lys Val Arg Ala Glu Ile Cys Leu Lys Arg
            740                 745                 750

Thr Glu Tyr Phe Lys Asn Gly Lys Leu Asn Ser Asp Ser Glu Ala Phe
        755                 760                 765

Leu Lys Asn Pro Gln Arg Met Lys Arg Phe Asp Gln Leu Phe Leu Glu
    770                 775                 780

Tyr Lys Glu Gln Lys Ala Leu Glu Ser Tyr Arg Gln Lys Ile Glu Gln
785                 790                 795                 800

Asn Ser Ile Met Lys Asn Gly Phe Gly Thr Val Leu Lys Gln Glu Asp
                805                 810                 815

Asp Asp Gln Leu Gln Phe His Asn Asp His Ser Leu Asn Gly Asn Glu
            820                 825                 830

Ala Phe Glu Lys Gln Pro Asn Asp Ile Glu Leu Asp Asp Thr Arg Phe
        835                 840                 845

Leu Gln Glu Tyr Asp Ile Ser Asn Ala Ile Pro Asp Ile Val Tyr Glu
    850                 855                 860

Gly Val Asn Thr Lys Thr Leu Asp Lys Met Glu Asp Ala Ser Val Asp
865                 870                 875                 880

Arg Met Leu Gln Asn Gly Ile Asn Lys Gln Ser Arg Phe Leu Ala Asn
                885                 890                 895

Lys Asp Leu Gly Leu Thr Pro Lys Met Asn Gln Asn Ile Thr Leu Ile
            900                 905                 910

Gln Gln Ile Arg His Ile Cys His Lys Ile Ser Leu Ile Arg Met Leu
        915                 920                 925

Gln Ser Pro Leu Ser Ala Gln Asn Ser Arg Ser Asn Pro Asn Ala Phe
    930                 935                 940

Leu Asn Asn His Ile Tyr Asn Tyr Thr Ile Ile Asp Asp Ser Leu Asp
945                 950                 955                 960

Ile Asp Pro Val Ser Gln Leu Pro Thr His Asp Tyr Lys Asn Asn Arg
                965                 970                 975

Glu Leu Ile Trp Lys Phe Met His Lys Asn Ile Ser Lys Val Ala Met
            980                 985                 990

Ala Asn Gly Phe Glu Thr Ala His  Pro Ser Ala Ile Asn  Met Leu Thr
        995                 1000                1005

Glu Ile  Ala Gly Asp Tyr Leu  Ser Asn Leu Ile Lys  Thr Leu Lys
    1010                1015                1020
```

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Leu His  His Glu Thr Asn Ser  Leu Asn Arg Gly Thr  Asn Val Glu
    1025                1030                1035

Met Leu  Gln Thr Thr Leu Leu  Glu Asn Gly Ile Asn  Arg Pro Asp
    1040                1045                1050

Asp Leu  Phe Ser Tyr Val Glu  Ser Glu Phe Gly Lys  Lys Thr Lys
    1055                1060                1065

Lys Leu  Gln Asp Ile Lys Gln  Lys Leu Glu Ser Phe  Leu Arg Ala
    1070                1075                1080

Leu Leu  Arg Pro Thr Leu Gln  Glu Leu Ser Glu Arg  Asn Phe Glu
    1085                1090                1095

Asp Glu  Ser Gln Ser Phe Phe  Thr Gly Asp Phe Ala  Ser Glu Leu
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Thr Gly  Glu Asp Phe Phe
    1115


<210> SEQ ID NO 20
<211> LENGTH: 3357
<212> TYPE: DNA
<213> ORGANISM: Saccharomyces cerevisiae

<400> SEQUENCE: 20

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gtcgttcttg aatacctgct gtcgatttca agtgaagaag acaaactgaa agcatgggac    180

tatttcttaa agggaaacat agcattaaat gtcgaaaaat catttccatt aacccaagaa    240

gaagaacatc acggagcggt ctctcctgcc gttgacacac gatcagatga tgtatcatca    300

caaacaatta aggacaataa caatactaat accaacacca gtatcagcaa tgaaaatcat    360

gttgaaaatg aaattgaaga taaaggcgat aacgcaatag caaatgaaga taattttgtg    420

aataatgacg aaagtgataa tgttgaagaa gacttattca aattagatct agaggacttg    480

aagcagcaaa taagcggaac aaggtttatt ggaaacttat ccttgaaaat cagatacgtc    540

ttgtggcagt gcgccataga ttatatatac tgtgatcgta atgagtttgg tgatgaaaat    600

gatacagaat acaccctatt agatgttgaa gagaaggagg aagaggaaat tggtaaaaat    660

gagaagccac aaaacaaaga aggtatttcg aagttcgccg aggatgaaga ttacgacgat    720

gaagacgaga actatgatga agacagtaca gacgtaaaaa atgtcgatga tcctccaaaa    780

aatctcgatt ctatttcctc ttctaatatc gaaattgacg atgaacgacg cttggtgcta    840

aatatctcaa tatcaaaaga aacactgtca aagttaaaaa caaataatgt agaagaaatt    900

atgggaaatt ggaacaaaat ttaccacagt tttgaatacg ataaagaaac tatgataaag    960

cgattaaaac ttgaagaaag cgataaaatg atagagaaag gaaagaagaa acgaagtcga   1020

agtgatttag aagcagctac cgatgaacaa gatcgcgaaa atacaaatga tgagccagat   1080

actaatcaaa aattgcccac tcctgaaggt tcaacattca gcgatactgg gaacaagcgc   1140

cccaaacaaa gtaatttaga tttaacagtc aatctaggca tcgaaaattt atcattaaag   1200

caccttctat catctatcca gcaaaaaaaa tcccaattag gaatatcaga ttacgaatta   1260

aaacatctga ttatggatgt cagaaaaaat cggtcaaaat ggacatcgga tgaaagaatt   1320

gggcaagagg aattatacga agcctgtgaa aaggttgttt tggaacttag aaactacact   1380

gagcattcta caccatttct gaataaagtg agcaaaagag aagcccccaa ttatcatcaa   1440

atcatcaaaa agtccatgga cctgaatact gttttaaaaa aactgaaaag ctttcaatat   1500

gactccaaac aagaatttgt agacgatatt atgctaatat ggaaaaattg tttgacctat   1560
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aattcagatc cttcacattt tttgagaggg catgctattg ctatgcagaa gaaatctctt   1620

cagttgattc gcatgattcc aaatatcaca atccgaaaca gggctgattt agaaaaggaa   1680

attgaagata tggaaaaaga caaagactac gaattagatg aggaagagga agttgctggt   1740

tctggaagaa aaggattgaa tatgggagct catatgttgg ccaaagagaa tggcaaggtg   1800

tcagaaaaag atagctctaa aaccgtcaag gatgaagcac caaccaatga tgacaaacta   1860

acttctgtca tccctgaggg ggaaaaagag aaagataaaa ctgcttcatc tactgtaacg   1920

gtacacgaaa atgtaaataa gaacgaaata aaagaaaatg ggaaaaatga agagcaagat   1980

atggttgagg aaagtagtaa gactgaggat tcatcaaaag atgctgatgc tgccaaaaag   2040

gatacggaag acggactaca agataaaact gcagaaaata aggaggctgg ggaaaataat   2100

gaagaggaag aggatgatga tgacgaagat gaagacgaag acatggtcga ctcccaatct   2160

tatttacttg aaaaggatga cgatagagac gatttggaaa tatccgtgtg gaaaactgta   2220

actgccaaag ttcgtgcgga aatttgctta aaaagaactg aatattttaa aaatggaaaa   2280

ttaaatagtg attcagaggc gtttttgaaa aacccacaaa gaatgaaaag gttcgaccag   2340

ctttttcttg aatataaaga gcagaaagct ttagaatcat atcgtcaaaa aatagagcaa   2400

aattccatta tgaaaaatgg ctttggaaca gtactaaaac aggaagacga tgaccaattg   2460

cagtttcata atgatcactc tttaaatgga aatgaagctt ttgaaaagca acccaatgat   2520

attgagttag atgataccag attcctacag gaatatgata ttagtaacgc cattcctgac   2580

atagtatacg agggagtaaa tactaaaaca ttagacaaga tggaagacgc ttccgtggac   2640

cgcatgcttc aaaatggtat caacaaacaa agcagatttc tggctaacaa ggatttagga   2700

ctaacaccta aaatgaacca aaatatcaca ctgattcagc aaattaggca catatgccat   2760

aaaatatccc tgatcagaat gttacagagc cctttatcgg ctcaaaactc cagaagcaat   2820

cccaacgctt tccttaacaa ccacatttat aattacacta ttattgatga ctcactcgat   2880

attgatccgg tgtcacagct tccaacgcat gattacaaaa acaacaggga gctgatatgg   2940

aaattcatgc ataagaacat atctaaggtt gctatggcca atgggtttga aactgcccat   3000

ccatcagcaa taaacatgct tactgaaatc gccggggatt acctatctaa tctgataaag   3060

actttgaagc ttcatcatga aactaactcc ttaaatagag gaacaaatgt ggaaatgctg   3120

caaacaacac tgttggaaaa cggtatcaac aggccagacg atctattttc ctatgttgaa   3180

tctgaatttg gtaaaaaaac taagaaactt caggacatca aacagaaact agaaagcttt   3240

ttgagagcct tattaaggcc aactttgcag gagttgtccg agagaaactt tgaagacgag   3300

agccaaagct tttttacagg tgactttgcc agcgaattga ctggtgaaga cttcttt      3357
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<210> SEQ ID NO 21
<211> LENGTH: 337
<212> TYPE: PRT
<213> ORGANISM: Saccharomyces cerevisiae

<400> SEQUENCE: 21

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Val Ser Gly Glu Ile Asn Asp Pro Pro Val Glu Thr Thr Ser Leu Ile
            20                  25                  30

Glu Asp Ile Val Arg Gly Gln Val Ile Glu Ile Leu Leu Gln Ser Asn
        35                  40                  45

Lys Thr Ala His Leu Arg Gly Ser Arg Ser Ile Leu Pro Glu Asp Val
    50                  55                  60
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Ile Phe Leu Ile Arg His Asp Lys Ala Lys Val Asn Arg Leu Arg Thr
65                  70                  75                  80

Tyr Leu Ser Trp Lys Asp Leu Arg Lys Asn Ala Lys Asp Gln Asp Ala
                85                  90                  95

Ser Ala Gly Val Ala Ser Gly Thr Gly Asn Pro Gly Ala Gly Gly Glu
            100                 105                 110

Asp Asp Leu Lys Lys Ala Gly Gly Gly Glu Lys Asp Glu Lys Asp Gly
        115                 120                 125

Gly Asn Met Met Lys Val Lys Lys Ser Gln Ile Lys Leu Pro Trp Glu
    130                 135                 140

Leu Gln Phe Met Phe Asn Glu His Pro Leu Glu Asn Asn Asp Asp Asn
145                 150                 155                 160

Asp Asp Met Asp Glu Asp Glu Arg Glu Ala Asn Ile Val Thr Leu Lys
                165                 170                 175

Arg Leu Lys Met Ala Asp Asp Arg Thr Arg Asn Met Thr Lys Glu Glu
            180                 185                 190

Tyr Val His Trp Ser Asp Cys Arg Gln Ala Ser Phe Thr Phe Arg Lys
        195                 200                 205

Asn Lys Arg Phe Lys Asp Trp Ser Gly Ile Ser Gln Leu Thr Glu Gly
    210                 215                 220

Lys Pro His Asp Asp Val Ile Asp Ile Leu Gly Phe Leu Thr Phe Glu
225                 230                 235                 240

Ile Val Cys Ser Leu Thr Glu Thr Ala Leu Lys Ile Lys Gln Arg Glu
                245                 250                 255

Gln Val Leu Gln Thr Gln Lys Asp Lys Ser Gln Gln Ser Ser Gln Asp
            260                 265                 270

Asn Thr Asn Phe Glu Phe Ala Ser Ser Thr Leu His Arg Lys Lys Arg
        275                 280                 285

Leu Phe Asp Gly Pro Glu Asn Val Ile Asn Pro Leu Lys Pro Arg His
    290                 295                 300

Ile Glu Glu Ala Trp Arg Val Leu Gln Thr Ile Asp Met Arg His Arg
305                 310                 315                 320

Ala Leu Thr Asn Phe Lys Gly Gly Arg Leu Ser Ser Lys Pro Ile Ile
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Met
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<210> SEQ ID NO 22
<211> LENGTH: 1014
<212> TYPE: DNA
<213> ORGANISM: Saccharomyces cerevisiae

<400> SEQUENCE: 22

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atagaaattc ttttacagtc aaacaaaacg gcgcatctta ggggaagtag gagcattctc    180

cctgaagacg tcatttttctt gatcagacac gacaaggcca aagtcaatcg tttgagaaca    240

tatctgtcat ggaaggattt gcgtaaaaac gccaaggacc aagatgctag tgccggtgta    300

gcgagtggca ctggaaatcc tggggcaggt ggtgaagatg atttgaaaaa agcaggtggt    360

ggcgagaaag acgaaaaaga tggtggaaac atgatgaagg tcaagaaatc ccaaattaag    420

ctgccatggg aattgcagtt tatgttcaat gaacatcctt tagaaaataa tgacgacaat    480

gatgatatgg atgaggatga acgagaagct aatatagtca ctttgaaaag gctgaaaatg    540
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gctgacgata gaacacgaaa catgactaaa gaggagtacg tgcattggtc cgattgtcga	600
caggcaagtt ttacatttag gaagaataaa aggttcaagg actggtctgg aatttcgcaa	660
ttaactgagg ggaaacccca tgatgatgtg attgatatac tggggtttct aacttttgag	720
attgtctgtt ctttgacgga aacagctctg aaaatcaaac aaagagaaca ggtattacag	780
actcaaaagg acaaatccca gcaatctagc caagataata ctaactttga atttgcatca	840
tccacattac atagaaagaa aagattattt gatggacctg aaaatgttat aaacccgctc	900
aaaccaaggc atatagagga agcctggaga gtactacaaa caattgacat gaggcatagg	960
gctttgacca actttaaagg tggtagactc agttctaaac caattatcat gtaa	1014

The invention claimed is:

1. A method for increasing a chronological lifespan of a cell comprising disrupting a function the Spt-Ada-Gcn5-Acetyltransferase complex in said cell, wherein the complex is disrupted by disrupting the function of the Spt7 gene or homologue thereof.

2. The method according to claim **1** wherein the at least one complex is directly or indirectly disrupted.

3. The method according to claim **1**, wherein the function of the gene is disrupted by iRNA.

4. The method according to claim **1**, wherein the function of the gene is disrupted at a transcriptional/DNA level.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,628,922 B2
APPLICATION NO. : 13/382629
DATED : January 14, 2014
INVENTOR(S) : Elizabeth Jane Mellor

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Column 111, line 23, Claim 2 should read:

2. The method according to claim 1 wherein the complex is directly or indirectly disrupted.

Signed and Sealed this
Fifth Day of August, 2014

Michelle K. Lee

Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office