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(57) ABSTRACT

The invention includes isolated nucleotide molecules that are differentially expressed in a native fungus exhibiting a first morphology relative to the native fungus exhibiting a second morphology. The invention includes a method of enhancing a bioprocess utilizing a fungus. A transformed fungus is produced by transforming a fungus with a recombinant nucleotide molecule. The recombinant nucleotide molecule contains an isolated nucleotide sequence linked operably to a promoter. The nucleotide sequence is expressed to promote a first morphology. The first morphology of the transformed fungus enhances a bioprocess relative to the bioprocess utilizing a second morphology.

2 Claims, 16 Drawing Sheets
OTHER PUBLICATIONS


Schoeffel R E A M et al., “FEM1, a Fusarium oxysporum glycoprotein that is covalently linked to the cell wall matrix and is conserved in filamentous fungi” MGG Molecular Genetics and Genomics, vol. 265, No. 1, May 1, 2001, pp. 143-152.


* cited by examiner
Relative amount of mRNA (% of mRNA at 20 min and 10 ppb Mn^{2+})
1. PROVIDE ISOLATED POLYNUCLEOTIDE

2. FORM RECOMBINANT POLYNUCLEOTIDE

3. TRANSFORMATION OF A FUNGUS

4. TRANSCRIPT HYBRIDIZATION AND SUPPRESSION OF TRANSLATION

5. EXPRESSION OF A POLYPEPTIDE ENCODED BY THE RECOMBINANT POLYNUCLEOTIDE
ISOLATED POLYNUCLEOTIDES AND METHODS OF PROMOTING A MORPHOLOGY IN A FUNGUS

RELATED PATENT DATA

This patent claims benefit of priority under 35 U.S.C. §119 to U.S. Provisional Patent Ser. No. 60/382,132, which was filed May 20, 2002.

CONTRACTUAL ORIGIN OF THE INVENTION

This invention was made with Government support under contract DE-AC0676RLO-1830, awarded by the U.S. Department of Energy. The Government has certain rights in this invention.

TECHNICAL FIELD

The invention pertains to isolated polynucleotide molecules, recombinant polynucleotide constructs, and methods of promoting a morphology in a fungus.

BACKGROUND OF THE INVENTION

Fungi are becoming increasingly utilized for production of numerous commercially useful products. A type of fungi known as "filamentous" fungi are currently used for the industrial scale production of metabolites such as antibiotics (penicillins and cephalosporins, for example) and organic acids (citric and fumaric acids for example). Filamentous fungi are additionally useful for the industrial production of enzymes such as, for example, proteases and lipases.

Utilization of a filamentous fungus species for production of desired compounds often involves growing submerged cultures of the fungus. Filamentous fungi can exhibit numerous morphologies in submerged cultures, one of which is the filamentous morphology. When fungi in culture exhibit a filamentous morphology, the filamentous growth can increase the viscosity of the culture medium. The increased viscosity can affect mass transfer and aeration properties of the culture, can cause mixing problems in a bioreactor, and can typically be accompanied by decreased productivity.

Alternatively, "filamentous" fungi can exhibit a pellet morphology. In contrast to cultures of fungi exhibiting a filamentous morphology, the viscosity of cultures of fungi exhibiting a pellet morphology can be relatively low and can utilize less power for mixing and aeration of the culture. For many products, for example citric acid, itaconic acid, statins, penicillins, and various enzymes, productivity can be enhanced utilizing fungus exhibiting a pellet morphology relative to fungus exhibiting a filamentous morphology. However, at least in certain fungal species, production of peptidase enzyme or fumaric acid, for example, can be enhanced by utilizing a fungus exhibiting a filamentous morphology.

It would be desirable to develop methods to promote a desired morphology in a fungus and to develop methods for influencing or controlling morphologies exhibited by a fungus in a culture to optimize productivity.

SUMMARY OF THE INVENTION

In one aspect, the invention encompasses a method of enhancing a bioprocess utilizing a fungus. A transformed fungus is produced by transforming a fungus with a recombinant polynucleotide molecule. The recombinant polynucleotide molecule contains an isolated polynucleotide sequence linked operably to a promoter. A polypeptide encoded by the polynucleotide sequence is expressed to promote a pellet morphology. The pelleted morphology of the transformed fungus enhances a bioprocess relative to the bioprocess utilizing a filamentous morphology of the transformed fungus.

In one aspect, the invention encompasses a method of promoting a morphology of a fungus and enhancing productivity of a bioprocess. A fungus is transformed with an antisense oriented polynucleotide sequence complimentary to a gene sequence. A transcription product of the polynucleotide sequence hybridizes to mRNA and thereby suppresses expression of the gene. The gene suppression promotes a morphology and enhances a bioprocess relative to the bioprocess in an alternative fungal morphology.

BRIEF DESCRIPTION OF THE DRAWINGS

Preferred embodiments of the invention are described below with reference to the following accompanying drawings.

FIG. 1 shows the results of Northern blot analysis of the transcriptional level of the native A. niger gene corresponding to the Balu-4 cDNA sequence set forth in SEQ ID NO:1. Lanes 1, 2 and 3 reflect transcription levels in the pellet morphology. Transcription levels in the filamentous morphology are shown at 20 minutes (lane 4), 40 minutes (lane 5) and 120 minutes (lane 6) after inducing the filamentous morphology.

FIG. 2 shows the alignment and comparison of the predicted amino acid sequence of A. niger Balu-4, SEQ ID NO:2 (top sequence) and the amino acid sequence of Emericella nidulans G-protein beta subunit, SEQ ID NO:3 (bottom sequence).

FIG. 3 shows the results of Northern blot analysis of transcription levels of the native A. niger gene corresponding to the Balu-42 cDNA sequence set forth in SEQ ID NO:4. Lanes 1, 2 and 3 reflect transcription levels in the pellet morphology. Transcription levels in the filamentous morphology are shown at 20 minutes (lane 4), 40 minutes (lane 5) and 120 minutes (lane 6) after inducing the filamentous morphology.

FIG. 4 shows the results of Northern blot analysis of transcription levels of the native A. niger gene corresponding to the Balu-42 cDNA sequence set forth in SEQ ID NO:5. Lanes 1, 2 and 3 reflect transcription levels in the pellet morphology. Transcription levels in the filamentous morphology are shown at 20 minutes (lane 4), 40 minutes (lane 5) and 120 minutes (lane 6) after inducing the filamentous morphology.

FIG. 5 shows the results of Northern blot analysis of transcription levels of the native A. niger gene corresponding to the Balu-43 cDNA sequence set forth in SEQ ID NO:6. Lanes 1, 2 and 3 reflect transcription levels in the pellet morphology. Transcription levels in the filamentous morphology are shown at 20 minutes (lane 4), 40 minutes (lane 5) and 120 minutes (lane 6) after inducing the filamentous morphology.

FIG. 6 shows the alignment and comparison of the predicted amino acid sequence of A. niger Bsa-43, SEQ ID NO:7 (top sequence), and the amino acid sequence of the Homo sapiens lysosomal peptatin insensitive protease, SEQ ID NO:8 (bottom sequence).
FIG. 7 shows the results of Northern blot analysis of transcription levels of the native A. niger gene corresponding to the Brsa-47 cDNA sequence set forth in SEQ ID NO.:12. Lanes 1, 2 and 3 reflect transcription levels in the pellet morphology. Transcription levels in the filamentous morphology are shown at 20 minutes (lane 4), 40 minutes (lane 5) and 120 minutes (lane 6) after inducing the filamentous morphology.

FIG. 8 shows the alignment and comparison of the predicted amino acid sequence of A. niger Brsa-47, SEQ ID NO.:14 (top sequence), and the amino acid sequence of Sclerotium rolfsii Myo-inositol 1-phosphate synthase, SEQ ID NO.:15 (bottom sequence).

FIG. 9 shows the results of Northern blot analysis of transcription levels of the native A. niger gene corresponding to the Brsa-109 cDNA sequence set forth in SEQ ID NO.:16. Lanes 1, 2 and 3 reflect transcription levels in the pellet morphology. Transcription levels in the filamentous morphology are shown at 20 minutes (lane 4), 40 minutes (lane 5) and 120 minutes (lane 6) after inducing the filamentous morphology.

FIG. 10 shows the results of Northern blot analysis of transcription levels of the native A. niger gene corresponding to the Brsa-118 cDNA sequence set forth in SEQ ID NO.:18. Lanes 1, 2 and 3 reflect transcription levels in the pellet morphology. Transcription levels in the filamentous morphology are shown at 20 minutes (lane 4), 40 minutes (lane 5) and 120 minutes (lane 6) after inducing the filamentous morphology.

FIG. 11 shows the alignment and comparison of the predicted amino acid sequence of A. niger Brsa-118, SEQ ID NO.:20 (top sequence), and the Neurospora crassa probable hydroxymethylglutaryl-CoA synthase, SEQ ID NO.:21 (bottom sequence).

FIG. 12 shows the results of Northern blot analysis of transcription levels of the native A. niger gene corresponding to the Arsa-7 cDNA sequence set forth in SEQ ID NO.:22. Lanes 1, 2 and 3 reflect transcription levels in the pellet morphology. Transcription levels in the filamentous morphology are shown at 20 minutes (lane 4), 40 minutes (lane 5) and 120 minutes (lane 6) after inducing the filamentous morphology.

FIG. 13 shows the results of Northern blot analysis of transcription levels of the native A. niger gene corresponding to the Arsa-48 cDNA sequence set forth in SEQ ID NO.:24. Transcription levels in the filamentous morphology are shown at 20 minutes (lane 4), 40 minutes (lane 5) and 120 minutes (lane 6) after inducing the filamentous morphology.

FIG. 14 shows the results of Northern blot analysis of transcription levels of the native A. niger gene corresponding to the A-37 cDNA sequence set forth in SEQ ID NO.:26. Lanes 1, 2 and 3 reflect transcription levels in the pellet morphology. Transcription levels in the filamentous morphology are shown at 20 minutes (lane 4), 40 minutes (lane 5) and 120 minutes (lane 6) after inducing the filamentous morphology.

FIG. 15 shows the results of Northern blot analysis of transcription levels of the native A. niger gene corresponding to the A-90 cDNA sequence set forth in SEQ ID NO.:28. Lanes 1, 2 and 3 reflect transcription levels in the pellet morphology. Transcription levels in the filamentous morphology are shown at 20 minutes (lane 4), 40 minutes (lane 5) and 120 minutes (lane 6) after inducing the filamentous morphology.

FIG. 16 shows the results of Northern blot analysis of transcription levels of the native A. niger gene corresponding to the Arsa-43 cDNA sequence set forth in SEQ ID NO.:33. Lanes 1, 2 and 3 reflect transcription levels in the pellet morphology. Transcription levels in the filamentous morphology are shown at 20 minutes (lane 4), 40 minutes (lane 5) and 120 minutes (lane 6) after inducing the filamentous morphology.

FIG. 17 shows the alignment and comparison of the predicted amino acid sequence of A. niger Arsa-43, SEQ ID NO.:34 (top sequence), and the Aspergillus nidulans polyubiquitin protein, SEQ ID NO.:35 (bottom sequence).

FIG. 18 shows the results of Northern blot analysis of transcription levels of the native A. niger gene corresponding to the Arsa-10 cDNA partial sequence set forth in SEQ ID NO.:36. Lanes 1, 2 and 3 reflect transcription levels in the pellet morphology. Transcription levels in the filamentous morphology are shown at 20 minutes (lane 4), 40 minutes (lane 5) and 120 minutes (lane 6) after inducing the filamentous morphology.

FIG. 19 shows the results of Northern blot analysis of transcription levels of the native A. niger gene corresponding to the Arsa-27 cDNA partial sequence set forth in SEQ ID NO.:37. Lanes 1, 2 and 3 reflect transcription levels in the pellet morphology. Transcription levels in the filamentous morphology are shown at 20 minutes (lane 4), 40 minutes (lane 5) and 120 minutes (lane 6) after inducing the filamentous morphology.

FIG. 20 shows a comparison of enhanced expression levels in filamentous morphology (right) relative to the pellet morphology (left) of native A. niger for each of the B. thuringiensis, B. subtilis, B. subtilis, B. thuringiensis, B. subtilis, and B. subtilis genes.

FIG. 21 shows a comparison of enhanced expression levels in the pellet morphology (left) relative to filamentous morphology (right) of native A. niger for each of the Arsa-7, Arsa-10, Arsa-27, Arsa-43 and A-90 genes.

FIG. 22 shows the results of Northern blot analysis of transcription levels of the native A. niger genes corresponding to the Arsa-4, Arsa-42, Arsa-25, Arsa-47, Arsa-109, and Arsa-118 genes.

FIG. 23 shows the results of Northern blot analysis of transcription levels of the native A. niger genes corresponding to the Arsa-7, Arsa-37, Arsa-48, and A-90 cDNA sequences set forth in SEQ ID NOs.:22, 24, 26 and 28, respectively. Panel (A) shows transcription levels in native A. niger grown in 10 ppb Mn^2+ (pellet morphology) for 14 hr (lane 1), 24 hr (lane 2), 48 hr (lane 3), 72 hr (lane 4), 96 hr (lane 5) and 120 hr (lane 6). Panel (B) shows transcription levels in native A. niger grown in 1000 ppb Mn^2+ (filamentous morphology) for 1 hr (lane 1), 2 hr (lane 2), 24 hr (lane 3), 36 hr (lane 4), 72 hr (lane 5) and 108 hr (lane 6).

FIG. 24 is a flowchart diagram illustrating a particular aspect of the present invention.

FIG. 25 shows suppression results for A. niger transformed with antisense oriented polynucleotide sequences complimentary to Bait-l-(Panel A), Brsa-25 (Panel B) and Brsa-118 (Panel C). Each panel compares morphologies of control A. niger (left) and transformed A. niger (right) containing the corresponding antisense DNA construct grown in 15 ppb Mn^2+ medium.
FIG. 26 shows suppression results for *A. niger* transformed with antisense oriented polynucleotide sequences complimentary to cDNAs corresponding to Arsa-7 (Panel A), A-37 (Panel B) and A-90 (Panel C). Each panel compares morphologies of control *A. niger* (left) and transformed *A. niger* (right) grown in 12 ppb Mn²⁺ medium.

FIG. 27 shows the citric acid production of control *A. niger* and transformed *A. niger* containing antisense polynucleotide sequence complimentary to Balu-42 (strain 2805) or complimentary to Bsa-118 (strain 2808). Panel (A) shows measured citric acid production for individual transformation experiments. Panel (B) shows averaged values of the data depicted in Panel (A).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The invention encompasses polynucleotides that can have differential expression in a native fungus. For purposes of the present description the term “expression” of a polynucleotide sequence can refer to the combined processes of transcription and translation, or can refer to a portion of the combined transcription and translation process. The term “differential expression” can refer to two or more differing levels of expression, or can refer to an absence in expression in a first instance relative to a presence of expression in a second instance.

The invention includes isolated polynucleotide molecules that can include a polynucleotide sequence that is differentially expressed in different morphologies exhibited by a native fungus. For purposes of the present description, the term “native” can refer to an organism that has not been genetically manipulated. The term “isolated” can refer to a naturally occurring molecule such as, for example, a polynucleotide or a polypeptide that has been recovered from the organism which produced it, or alternatively can refer to a synthetic molecule.

An isolated polynucleotide molecule according to the present invention can comprise a polynucleotide sequence that has an increased expression in a fungus exhibiting a pellet morphology relative to a lower level or an absence of expression in the filamentous morphology of the fungus. Alternatively, a polynucleotide molecule according to the present invention can comprise polynucleotide sequence having an increased expression level in a filamentous morphology of a native fungus relative to a lower level or absence of expression in the pellet morphology.

Isolated polynucleotides encompassed by the present invention can be isolated from any source fungus that is capable of exhibiting a filamentous morphology and a pellet morphology. A source fungus is not limited to a specific group of fungi and can be a member any of the three major fungal groups. An exemplary member of the Basidiomycetes group is *Phanerochaete chrysosporium*. Exemplary members of the group of Ascomycetes and Imperfect Fungus include *Aspergillus niger*, *Aspergillus oryzae*, *Aspergillus terreus*, *Emericella nidulans*, *Neurospora crassa*, *Fusarium oxysporum*, *Penicillium chrysogenum*, and *Trichoderma reesei*. Exemplary members of the Zygomycetes group include *Rhizomucor miehei* and *Rhizopus oryzae*.

An exemplary isolated polynucleotide molecule encompassed by the present invention can comprise a polynucleotide sequence isolated from *A. niger* that is differentially expressed in the filamentous morphology of native *A. niger* relative to the pellet morphology of native *A. niger*. The differentially expressed polynucleotide sequence can comprise, for example, a sequence as set forth in any of SEQ ID NOs.:1, 4, 6, 8, 12, 16, 18, 22, 24, 26, 28, 33, 36 and 37, or can comprise a sequence complimentary to any of those sequences. Each of the polynucleotide sequences set forth in SEQ ID NOs.:1, 4, 6, 8, 12, 16, 18, 22, 24, 26, 28, 33, 36 and 37, corresponds to the sequence determined from a full-length cDNA molecule prepared according to methods discussed below, with SEQ ID NOs.:36 and 37 being partial sequences determined from full length cDNA. It is to be understood that the isolation methods and techniques discussed herein are exemplary and that numerous conventional techniques can be utilized for producing the isolated polynucleotide molecules of the present invention.

Full-length cDNA molecules comprising the polynucleotide sequences set forth in SEQ ID NOs.:1, 4, 6, 8, 12, 16, 18, 22, 24, 26, 28, 33, 36 and 37, are obtained from *A. niger* strain ATCC11414 utilizing suppression subtractive hybridization techniques (Diatchenko et al., *Proceedings National Academy of Science U.S.A.* Vol. 93, pp. 6025-6030, 1996), in conjunction with PCR-SELECT™ cDNA subtraction kit (CLONTECH, Palo Alto, Calif.). Two suppression subtractive cDNA libraries are constructed. A first cDNA library is constructed utilizing cDNA obtained from *A. niger* exhibiting the pellet type morphology as tester and cDNA obtained from *A. niger* exhibiting the filamentous morphology as driver. The driver/tester ratio is increased threefold over the ratio suggested by the subtraction kit manual.

A second suppression subtractive cDNA library is created utilizing cDNA obtained from *A. niger* exhibiting the filamentous morphology as tester and utilizing cDNA obtained from *A. niger* exhibiting pellet morphology as driver. A first cDNA pool is generated from the first library and a second cDNA pool is generated from the second library. Differentially expressed cDNAs that are specifically present or enhanced in the pellet morphology are isolated from the first cDNA library by hybridization utilizing the first cDNA pool as probes and independently hybridizing the second cDNA pool as probes. Isolation of cDNA that is enhanced or specific to the filamentous morphology of *A. niger* is achieved by independently hybridizing the second cDNA library utilizing the first cDNA pool and the second cDNA pool as probes.

The segments of differentially expressed cDNAs that are isolated by suppression subtractive hybridization are selected for DNA sequencing. Sequencing of the segments is performed utilizing single pass sequencing with the 17-2 primer. The DNA fragments isolated by the suppression subtractive hybridization are used to design pairs of gene specific primers for utilization in isolating full-length cDNAs.

Full-length cDNA isolation is achieved utilizing the marathon cDNA amplification kit and the ADVANTAGE® cDNA polymerase (CLONTECH, Palo Alto, Calif.). The gene specific primers designed from the suppression subtractive hybridization clones are utilized for performing rapid amplification of cDNA ends PCR (RACE-PCR). The sequence of full-length cDNAs is determined using conventional automated DNA sequencing methods.

Twelve full-length cDNA clones and two partial-length cDNA clones are produced and sequenced according to the methods discussed above. The resulting sequences are presented as follows. The sequence of the Balu-4 cDNA is set forth in SEQ ID NO.:1; the sequence of the Balu-42 cDNA is set forth in SEQ ID NO.:4; the sequence of the Bsa-25 cDNA is set forth in SEQ ID NO.:6; the sequence of the Bsa-43 cDNA is set forth in SEQ ID NO.:8; the sequence of the Bsa-47 cDNA is set forth in SEQ ID NO.:12; the sequence of the Bsa-109 cDNA is set forth in SEQ ID NO.:16; the sequence of the Bsa-118 cDNA is set forth in SEQ ID NO.:
18; the sequence of the Aars7 cDNA is set forth in SEQ ID NO.:22; the sequence of the Aars-48 cDNA is set forth in SEQ ID NO.:24; the sequence of the A-37 cDNA is set forth in SEQ ID NO.:26; the sequence of the A-90 cDNA is set forth in SEQ ID NO.:28; the sequence of the Aars-43 cDNA is set forth in SEQ ID NO.:33; the partial sequence of the Aars-10 cDNA is set forth in SEQ ID NO.:36; and the partial sequence of the Aars-27 cDNA is set forth in SEQ ID NO.:37.

The amino acid sequence of each of the fourteen determined polyadenylate sequences is predicted utilizing the known genetic code. Homology searches are performed utilizing BLASTP to investigate homology between a predicted amino acid sequence and the sequences in the NCBI non-redundant GenBank CDS. All homology searches are conducted utilizing a threshold E value of E=0.005. Accordingly, the results of each BLAST homology search (discussed below) are based upon this initial threshold value.

Northern blot analysis is utilized to analyze the expression levels of the genes in native A. niger corresponding to each of the fourteen cDNA clones. The expression of each gene by A. niger exhibiting filamentous morphology is compared to the expression of the same gene in A. niger exhibiting the pellet morphology. For expression analysis, A. niger is initially grown in a culture medium containing less than or equal to about 12 parts per billion (ppb) Mn^-2+ for 12 hours. After the initial 12 hours of growth the culture is divided into two halves, the first half is maintained at low Mn^-2+ concentration (less than or equal to about 12 ppb) and the other half is brought to a final concentration of approximately 1000 ppb Mn^-2+ (or in some instances to a final concentration of greater than or equal to about 15 ppb Mn^-2+). A. niger can be extremely sensitive to Mn^-2+ concentration. At Mn^-2+ concentrations at or below about 12 ppb, native A. niger exhibits the pellet morphology, while at Mn^-2+ concentrations higher than about 12 ppb, native A. niger exhibits filamentous morphology. To simplify the present description, the point at which the culture is divided into two halves (after 12 hours of initial growth) can be referred to as time zero (t=0). Additionally, since the addition of Mn^-2+ to a final concentration of above 12 ppb promotes the filamentous morphology, the addition of Mn^-2+ can be referred to as filament induction.

Culture samples are collected at 20, 40, 60 and 120 minutes after time zero from both the non-induced culture (pellet morphology) and the induced culture (filamentous morphology). The samples are centrifuged to form culture pellets which are frozen with liquid nitrogen and stored at -80°C for future total RNA extraction.

Total RNA can be isolated from the frozen culture pellets utilizing conventional methods. After size fractionation of the total RNA sample by conventional gel electrophoresis techniques and subsequent transfer to a blotting membrane, the total RNA samples collected at each time point are analyzed using hybridization of probes that are synthesized by randomly priming the isolated suppression subtractive hybridization cDNA fragments or by randomly priming fragments of full-length cDNA digested with restriction endonuclease. Probes synthesis includes incorporation of [32P]-dCTP. Hybridization results of the Northern blots can be visualized by exposing the blots to x-ray film.

FIG. 1 shows the x-ray film exposure of a Northern blot analysis of the expression of the A. niger gene corresponding to Balu-4 SEQ ID NO.:1. Increased hybridization is apparent in mRNA samples taken from filamentous cultures (lanes 4, 5 and 6) relative to mRNA produced in pellet morphology (lanes 1-3). Fifteen micrograms (μg) of total RNA is used for each lane. The RNA samples utilized are obtained from post-t-0 pellet cultures at t=20 minutes (lane 1), t=40 minutes (lane 2) and t=120 minutes (lane 3); and from post-induction filamentous cultures at t=20 minutes (lane 4), t=40 minutes (lane 5) and t=120 minutes (lane 6). The total RNA used for each lane and the lane identification for each of the Northern blots discussed below is the same as that set forth for FIG. 1. The results shown in FIG. 1 indicate that Balu-4 is differentially expressed in native A. niger, with an increased level of expression detected in the filamentous morphology.

The predicted amino acid sequence of Balu-4 is set forth in SEQ ID NO.:2. The Balu-4 amino acid sequence is predicted from the Balu-4 cDNA sequence (SEQ ID NO.:1). As shown in FIG. 2, an amino acid sequence homology search utilizing BLASTP indicates that SEQ ID NO.:2 (top sequence) has a 97% identity with the amino acid sequence of a G-protein beta subunit of Emericella nidulans, SEQ ID NO.:3 (bottom sequence). Positions of sequence identity are indicated by the placement of the corresponding identical amino acid symbol between SEQ ID NO.:2 (top) and SEQ ID NO.:3 (bottom). The symbol "*" shown intermediate SEQ ID NO.:2 and SEQ ID NO.:3 indicates a conservative amino acid difference. For purposes of the present invention, a conservative amino acid difference or a conservative amino acid substitution can refer to a substitution of one amino acid by another amino acid with similar chemical properties. Additionally, the term “homology” can, in some instances, refer to an identical or a conservative amino acid.

The appearance of an open space between corresponding positions in SEQ ID NO.:2 and SEQ ID NO.:3 in FIG. 2 indicates a non-conservative amino acid difference between the two aligned sequences. Three sections of SEQ ID NO.:2 having relatively minimal identity with SEQ ID NO.:3 are set forth as SEQ ID NO.:30, 31 and 32. SEQ ID NO.:30 corresponds to amino acids 28-49 of SEQ ID NO.:2. SEQ ID NO.:31 corresponds to amino acids 194-209 of SEQ ID NO.:2. SEQ ID NO.:32 corresponds to amino acids 260-288 of SEQ ID NO.:2.

FIG. 3 shows the results of Northern blot analysis of the expression of the native gene corresponding to Balu-42, SEQ ID NO.:4. The increased detection of mRNA corresponding to Balu-42 in the filamentous morphology indicates that Balu42 is differentially expressed with increased expression in filaments relative to the pellet morphology of native A. niger.

SEQ ID NO.:5 corresponds to the Balu-42 amino acid sequence predicted from SEQ ID NO.:4. A BLASTP homology search is unable to identify homology between SEQ ID NO.:5 and any sequence in the searched database.

FIG. 4 shows the results of Northern blot analysis of the expression of the native gene corresponding to the Brsa-25 cDNA sequence set forth in SEQ ID NO.:6. The results indicate that Brsa-25 is differentially expressed with increased expression in the filamentous morphology of native A. niger relative to the pellet morphology.

The predicted amino acid sequence of Brsa-25 SEQ ID NO.:6 is set forth in SEQ ID NO.:7. A BLASTP homology search was unable to identify homology between SEQ ID NO.:7 and any sequence in the searched database.

FIG. 5 shows the results of the Northern blot analysis of the expression of the native gene corresponding to the Brsa-43 cDNA set forth in SEQ ID NO.:8. The Northern blot results indicate that Brsa-43 is differentially expressed with increased expression in the filamentous morphology of native A. niger relative to the pellet morphology.
NO.: 10 (top sequence) which has 31% identity to the amino acid sequence of human trippeptidyl-peptidase I precursor (lysosomal peptatin insensitive protease), SEQ ID NO.: 11 (bottom sequence). Indication of identity and homology between sequences is as discussed above with respect to FIG. 2.

Fig. 7 shows the results of Northern blot analysis of the expression of the native Bsa-47 gene corresponding to the cDNA sequence set forth in SEQ ID NO.: 12. The results indicate that Bsa-47 is differentially expressed, with increased expression levels apparent in the filamentous morphology relative to the pellet morphology of native A. niger.

The amino acid sequence of Bsa-47 as predicted from SEQ ID NO.: 12 is set forth in SEQ ID NO.: 13. Fig. 8 shows the BLASTP homology search results for SEQ ID NO.: 14 (top sequence) which corresponds to amino acids 26-530 of SEQ ID NO.: 13. The BLASTP results indicate that SEQ ID NO.: 14 has a 56% identity with the amino acid sequence of Myo-inositol 1-phosphate synthase from Sesamum indicum, SEQ ID NO.: 15 (bottom sequence).

The results of Northern blot analysis of the expression of the Bsa-109 gene in native A. niger corresponding to the cDNA sequence set forth in SEQ ID NO.: 16 is shown in FIG. 9. The results indicate that the Bsa-109 gene is differentially expressed, with increased expression detected in the filamentous morphology relative to the pellet morphology.

The Bsa-109 amino acid sequence predicted from SEQ ID NO.: 16 is set forth in SEQ ID NO.: 17. A BLASTP homology search is unable to identify homology between SEQ ID NO.: 19 and any sequence in the database.

Fig. 10 shows the results of Northern blot analysis of the expression of the Bsa-118 gene in native A. niger corresponding to the cDNA sequence set forth in SEQ ID NO.: 18. The results indicate that the Bsa-118 gene is differentially expressed, with increased expression in the filamentous morphology relative to the pellet morphology.

The amino acid sequence of Bsa-118 predicted from SEQ ID NO.: 18 is set forth in SEQ ID NO.: 19. Fig. 11 shows the BLASTP homology search results for Bsa-118. The results show that the predicted amino acid sequence of Bsa-118, SEQ ID NO.: 20 (top sequence), has 66% identity with the amino acid sequence of probable hydroxymethylglutaryl-CoA synthase from Neospora crassa, SEQ ID NO.: 21 (bottom sequence).

Fig. 12 shows the results of Northern blot analysis of the expression of the Arsa-7 gene in native A. niger corresponding to the cDNA sequence set forth in SEQ ID NO.: 22. The results indicate that the Arsa-7 gene is differentially expressed, with increased expression levels in the pellet morphology relative to expression levels in the filamentous morphology.

The amino acid sequence of Arsa-7 as predicted from SEQ ID NO.: 22 is set forth in SEQ ID NO.: 23. BLAST homology search results were unable to identify any sequences with homology to the predicted amino acid sequence of Arsa-7.

Fig. 13 shows the results of Northern blot analysis and the expression of the Arsa-48 gene in native A. niger corresponding to the cDNA sequence set forth in SEQ ID NO.: 24. The results indicate the Arsa-48 gene is differentially expressed, with increased expression levels occurring in the pellet morphology relative to the filamentous morphology.

The Arsa-48 amino acid sequence as predicted from SEQ ID NO.: 24, is set forth in SEQ ID NO.: 25. A BLASTP homology search was unable to identify homology between the Arsa-48 amino acid sequence and any other amino acid sequence in the searched database.

Fig. 14 shows the results of a Northern blot analysis of the expression of the A-37 gene in native A. niger corresponding to the cDNA sequence set forth in SEQ ID NO.: 26. The results indicate that the A-37 gene is differentially expressed with increased expression occurring in the pellet morphology relative to the expression level detected in the filamentous morphology.

The A-37 amino acid sequence as predicted from SEQ ID NO.: 26, is set forth in SEQ ID NO.: 27. The BLASTP homology search was unable to detect any homology between the predicted A-37 amino acid sequence and other amino acid sequences in the searched database.

Fig. 15 shows the results of Northern blot analysis of the expression of the A-90 gene in native A. niger corresponding to the cDNA sequence set forth in SEQ ID NO.: 28. The results indicate that A-90 is differentially expressed with an increased expression level occurring in the pellet morphology relative to the expression level detected in the filamentous morphology.

The amino acid sequence of A-90 as predicted from SEQ ID NO.: 28, is set forth in SEQ ID NO.: 29. A BLASTP homology search performed on SEQ ID NO.: 29 is unable to detect any homology with any other amino acid sequence in the database.

Fig. 16 shows the results of Northern blot analysis of the expression of the Arsa-43 gene in native A. niger corresponding to the cDNA sequence set forth in SEQ ID NO.: 33. The results indicate that the Arsa-43 gene is differentially expressed, with increased expression in the pellet morphology relative to the filamentous morphology.

The amino acid sequence of Arsa-43 predicted from SEQ ID NO.: 33 is set forth in SEQ ID NO.: 34. Fig. 17 shows the BLASTP homology search results for Arsa-43. The results show that the predicted amino acid sequence of Arsa-43, SEQ ID NO.: 34 (top sequence), has 96% identity with the amino acid sequence of the polyubiquitin protein from Aspergillus nidulans, SEQ ID NO.: 35 (bottom sequence).

Fig. 18 shows the results of Northern blot analysis of the expression of the Arsa-10 gene in native A. niger corresponding to the cDNA partial sequence set forth in SEQ ID NO.: 36. The results indicate that the Arsa-43 gene is differentially expressed, with increased expression in the pellet morphology relative to the filamentous morphology. Homology searching is unable to detect any homology between SEQ ID NO.: 36 and other polynucleotide sequences in the searched database.

Fig. 19 shows the results of Northern blot analysis of the expression of the Arsa-27 gene in native A. niger corresponding to the cDNA sequence set forth in SEQ ID NO.: 37. The results indicate that the Arsa-43 gene is differentially expressed, with increased expression in the pellet morphology relative to the filamentous morphology. Homology searching is unable to detect any homology between SEQ ID NO.: 37 and other polynucleotide sequences in the searched database.

Referring to FIGS. 20 and 21, such show bar-chart comparison of differential expression of various A. niger genes.

Fig. 20 shows transcript levels for genes Balu-4, Bsa-25, Bsa-43, Bsa-47, Bsa-109 and Bsa-118, which show increased expression in filamentous A. niger. Fig. 21 shows transcript levels for genes Arsa-7, Arsa-10, Arsa-27, A-37, Arsa-43, and A-90, which show increased expression in the pellet morphology of A. niger.

Additional expression analysis is conducted utilizing cultures grown for up to 5 days post t=0 (as defined above). Referring to FIG. 22, such shows the increased transcript levels for genes Balu-4, Balu-42, Bsa-25, Bsa-47, Bsa-109, and Bsa-118 in native A. niger grown in filamentous conditions (Panel B) as compared to transcript levels in A. niger.
grown in pellet conditions (Panel A). Referring to FIG. 23, such shows the increased transcript levels for genes Ars-a-7, A-37, Ars-a-48 and A-90 in native A. niger grown in pellet conditions (Panel A), as compared to levels of the corresponding transcript in filamentous cultures (Panel B).

In particular embodiments, the present invention encompasses isolated polypeptide molecules comprising an amino acid sequence set forth in any of SEQ ID NOs.: 2, 5, 7, 9, 13, 17, 19, 23, 25, 27, 29, 34, and 39, and functional equivalents thereof. For purposes of the present description, the term functional equivalent can refer to a truncated version or a conservatively substituted version of an amino acid sequence having substantially equivalent functional properties and/or biological activity relative to the non-truncated, non-substituted polypeptide. As will be understood by those skilled in the art, conventional methods can be utilized for truncating or introducing conservative amino acid substitutions into the amino acid sequences set forth in the sequence listing. Conventional methods are available that can be utilized for producing of the isolated polypeptides of the present invention.

In addition to the isolated polypeptide molecules discussed above, the present invention encompasses nucleotide sequences comprising alternative polynucleotide sequences that encode the amino acid sequences set forth in SEQ ID NOs.: 2, 5, 7, 9, 13, 17, 19, 23, 25, 27, 29, 34, or that encode functional equivalents of those amino acid sequences. The invention also encompasses amino acid sequences encoded by SEQ ID NOs.: 36 and 37, and functional equivalents, and alternate polynucleotide sequences encoding the amino acid sequences encoded by SEQ ID NOs.: 36 and 37. As will be understood by those skilled in the art, various modifications can be introduced into a polynucleotide sequence without affecting the resulting amino acid sequence due to the degenerate nature of the genetic code.

Various recombinant polynucleotide constructs are encompassed by the present invention. In particular embodiments, a recombinant polynucleotide construct according to the present invention can comprise any of the isolated polynucleotide sequences discussed above. All or part of any of the polynucleotide sequences discussed herein can be linked to a promoter, preferably operably linked to a promoter. Operable linkage of a polynucleotide to a promoter can form a recombinant polynucleotide construct that allows expression of the polynucleotide sequence to be controlled by the promoter. Alternatively, a sequence complimentary to at least a part of a sequence set forth in any one of SEQ ID NOs.: 1, 4, 6, 8, 12, 16, 18, 22, 24, 26, 28, 33, 36, and 37, can be utilized to form a recombinant polynucleotide, and can be incorporated in antisense orientation.

In particular aspects, the complementary sequence can comprise a portion of complementary sequence of sufficient length to enable suppression hybridization (discussed below). Although utilization of polynucleotide sequences of fewer than 30 nucleotides is contemplated, suppression hybridization can typically involve utilization of one or more polynucleotides having a length of greater than or equal to 30 nucleotides. Accordingly, the invention encompasses polynucleotide sequences comprising a fragment of any of the sequences set forth in any one of SEQ ID NOs.: 1, 4, 6, 8, 12, 16, 18, 22, 24, 26, 28, 33, 36, and 37, and complimentary fragments. Such fragments can preferably comprise a length of at least 30 nucleotides of the corresponding sequence, or complimentary sequence.

The invention also encompasses a vector comprising any of the isolated polynucleotide sequences discussed above. Vectors encompassed by the present invention are not limited to a particular type of vector and can be, for example, a plasmid, a cosmids or a viral vector. Vectors according to the present invention can be utilized for introducing into a host cell one or more of the isolated polynucleotide molecules discussed. The host cell is not limited to a particular cell type and can be, for example, a bacterium, a fungus, or a higher-eukaryotic cell. Alternatively, vectors encompassed by the present invention can be cloning vectors, expression vectors and/or integration vectors.

The invention also encompasses a transformed host cell and cell cultures which have been transformed to comprise any of the isolated polynucleotide molecules discussed above. Conventional cell transformation techniques can be utilized for introduction of the isolated polynucleotide into a desired host cell.

The present invention encompasses methods for promoting a morphology in a fungus. A process for promoting a morphology in a fungus is described with reference to a flowchart in FIG. 24. At initial step 100, an isolated polynucleotide is provided. The isolated polynucleotide from step 100 can comprise any of the isolated polynucleotides discussed above.

The isolated polynucleotide from step 100 can be used to form a recombinant polynucleotide in step 110. As discussed above, formation of the recombinant polynucleotide can comprise operably linking a promoter and the isolated polynucleotide sequence. Additionally, formation of a recombinant nucleotide step 110 can comprise formation of a vector which can be utilized to transform a fungus in step 120. Numerous fungi are available for utilization in transformation step 120. Preferably the fungus to be transformed is capable of exhibiting a filamentous morphology and is additionally capable of exhibiting a polynucleotide morphology. Exemplary fungi for purposes of step 120 can be, for example, any of the fungi discussed above with respect to source fungi.

After transformation step 120, a polypeptide encoded by the recombinant polynucleotide can be expressed from the transformed fungus in step 130. The expression in step 130 can promote a particular morphology of the fungus. The particular morphology promoted by the expression can be determined by the sequence of the isolated polynucleotide provided in step 100. For example, a filamentous morphology can be promoted by providing an isolated polynucleotide encoding a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOs.: 2, 5, 7, 9, 13, 17, and 19, and functional equivalents thereof. Alternatively, a polypeptide morphology can be promoted by providing an isolated polynucleotide in step 100 that encodes a polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOs.: 23, 25, 2729, and 34, or a functional equivalent thereof; or that encodes an amino acid sequence encoded by polynucleotide SEQ ID NO.: 36 or 37, or a functional equivalent thereof.

In an alternate embodiment of the present invention, a recombinant polynucleotide comprising an antisense oriented complimentary sequence (discussed above) can be utilized for transformation step 120. In a suppression step 140, the RNA produced from transcription of the antisense DNA can form an RNA duplex (dsRNA) with the native mRNA and thereby promote RNA degradation and/or inhibit or block translation of the mRNA. Accordingly, recombinant antisense constructs introduced in step 120 can suppress or block expression of the complementary gene to promote a desired morphology. For example, a polynucleotide construct comprising a sequence complimentary to a fragment or an entirety of any of SEQ ID NOs.: 1, 4, 6, 8, 12, 16 or 18 can be introduced in step 120. In step 140, the transcript produced from the antisense complimentary sequence can hybridize to
mRNA transcribed from genes Balu-4, Balu-42, Brsa-25, Brsa-43, Brsa-47, Brsa-109 or Brsa-118, respectively, and inhibit or block production of the corresponding protein product. Suppression of one or more of Balu-4, Balu-42, Brsa-25, Brsa-43, Brsa-47, Brsa-109 or Brsa-118 by methods in accordance with the present invention can promote pellet morphology in the transformed host. Similarly, polynucleotides having one or more sequences complementary to a fragment or an entirety of any of SEQ ID Nos: 22, 24, 26, 28, 33, 36, and 37, can be introduced in step 120, can inhibit or block expression of corresponding gene Arsa-7, Arsa-48, A-37, A-90, Arsa-43, Arsa-10 and Arsa-27. Suppression of one or more of Arsa-7, Arsa-48, A-37, A-90, Arsa-43, Arsa-10 and Arsa-27 in step 140 by methods in accordance with the present invention can promote filamentous morphology in the transformed host.

Although the process shown in FIG. 24 was discussed in terms of providing a single isolated polynucleotide in step 100, it is to be understood that the invention encompasses providing two or more of the isolated polynucleotide sequences discussed above. Additionally, it is to be understood that isolated polynucleotide sequences can be provided in step 100 wherein at least one of the isolated polynucleotides provided can promote pellet morphology when expressed and at least one other provided isolated polynucleotide can promote filamentous morphology when expressed. By operably linking differing isolated polynucleotides to differing inducible promoters in step 110, and using multiple recombinant polynucleotides for transformation step 120, it can be possible to selectively promote either the filamentous morphology or the pellet morphology by inducing expression in step 130 or 140.

It can be advantageous to promote a particular morphology in a fungus since utilization of a particular fungus morphology can enhance a bioprocess in a fungus culture. For example, utilization of a pellet form of a fungus can enhance various bioprocesses such as, for example, expressing hemicellulose, expressing cellulase, expressing lignase, converting biomass to alcohol, producing organic acids, producing glucoamylase, producing penicillin and producing lovastatin. Alternatively, utilization of filamentous fungal cultures can enhance bioprocesses such as fumaric acid production or peptidase enzyme production.

The process shown in FIG. 24 can be utilized to produce a transformed fungus and to promote a pellet morphology in the transformed fungus which can be utilized to enhance production of a desired product in a culture containing the transformed fungus relative to non-transformed fungus cultures under otherwise identical conditions. Alternatively, the process can be utilized to produce a transformed fungus and to promote a filamentous morphology in the transformed fungus. The promoted filament morphology can enhance production of a desired product in a culture containing the transformed fungus relative to non-transformed fungus culture under otherwise substantially identical conditions.

The invention also contemplates co-introduction of one or more polynucleotides encoding one or more proteins of interest along with the morphology promoting construct discussed above. The protein of interest can be native to the host or can be from a different fungal or non-fungal species. Where the protein(s) of interest have increased expression and/or activity in a first morphology relative to a second morphology, the morphology promoting construct co-introduced can preferably promote the first morphology. A protein of interest may be one that can be collected from the culture or can be one that is involved in a bioprocess that produces a desired product or compound.

**EXAMPLES**

**Example 1**

General Methods for DNA Isolation and Functional Analysis

*Escherichia coli* (E. coli) strains DH5α and JM109 are used as hosts for cloning experiments. *Agrobacterium tumefaciens* strain AGL0 is utilized as host for binary vectors and transformation of *A. niger*.

For isolation of morphology associated genes by suppression subtractive hybridization (SSH), total RNA is isolated from *A. niger* according to the modified acid phenol-guanidinium isothiocyanate-chloroform extraction method described by Chomczynski and Sacchi (Anal. Biochem. 162: 156-159 (1987)). The SSH is performed utilizing the PCR-SELECT™ cDNA subtraction kit (CLONTECH, Palo Alto Calif.) as described by the manufacturer, with the exception that the amount of driver cDNA relative to tester utilized was tripled for each of the first and the second hybridizations.

Morphology associated clones are identified by differential screening of SSH cDNA libraries. Two oligonucleotides are designed against each newly isolated clone sequence. Rapid amplification of cDNA and PCR (RACE-PCR) is performed to isolate the 5’-end and the 3’-end of each cDNA clone. Fungal transformation is achieved utilizing the Bgl II/Xba I pGPD-A hph-trpC fragment in pAN7-1 (Punt and van der Honde, Methods Enzymol. 216: 447-57 (1992)), inserted into binary vector pGA482 (An et al., *Binary Vectors* in *Plant Molecular Biology Manual*, Gelvin and Schilperoort (1998), at pp A3/1-9). Introduction of constructs based on pGA482 into *Agrobacterium tumefaciens* strain AGL0 is conducted utilizing the freeze-and-thaw method (Ebert et al., Proc. Natl. Acad. Sci., USA 84: 5745-5749 (1987)). Plasmids are isolated from the transformed *A. tumefaciens*, are digested with various restriction enzymes, and are analyzed utilizing agarose gel electrophoresis to confirm transformation. Fungal transformations are performed as described by Groot et al. (Nat. Biotechnol. 18: 839-42 (1998). At least fifteen independently transformed fungi were selected and grown on agar minimum media containing 250 μg/ml of hygromycin, and 250 μg/ml cefotaxin for each transgenic event.

**Example 2**

Promoting a Morphology Using Antisense Expression

Individual transgene expression vectors are constructed to comprise polynucleotide sequence complimentary to one the following: Balu-42 (SEQ ID No. 4); Brsa-25 (SEQ ID No.: 6); Brsa-118 (SEQ ID No.: 18); Arsa-7 (SEQ ID No.: 22); A-37 (SEQ ID No.: 26); and A-90 (SEQ ID No.: 28). The complimentary sequences are incorporated into the vectors in antisense orientation under the control of *A. nidulans* phosphoglycerate dehydrogenase (pgdA) promoter and *A. nidulans* trpC terminator. The constructed vectors are independently introduced into *A. niger* utilizing *Agrobacterium tumefaciens* mediated transformation. Control *A. niger* is prepared by transformation with binary vector without incorporated antisense sequence.

Referring to FIG. 25, such shows the promotion of the pellet morphology in transgenic *A. niger* expressing antisense Balu-42, Brsa-25 and Brsa-118 (right), as compared to control *A. niger* cultured under identical conditions. FIG. 26
shows the promotion of filamentous morphology in transgenic A. niger expressing antisense Arsa-7, A-37 and A-90 (right), as compared to control A. niger cultured under identical conditions.

Example 3

Morphology Enhanced Bio-production

Transgenic A. niger comprising antisense complimentary Bnu-42 (strain 2805) or Bna-118 (strain 2808) is prepared as described in Example 1. Multiple independently transformed cultures of each strain and multiple control cultures (prepared as described above) were grown at 30°C for about 50 hours. Referring to FIG. 27, Panel A shows the citric acid production for individual cultures of transformed strains 2805 (Bnu-42) and 2808 (Bna-118), and for control A. niger. Panel B shows the average citric acid production for cultures of strains 2805 and 2808 relative to control cultures.

The results indicate that the methods and sequences of the invention can be utilized to promote morphology in fungi. The promotion of a morphology by methodology of the invention can be used for enhancing production of protein and/or enhancing a bioprocess utilizing transgenic fungi.

In compliance with the statute, the invention has been described in language more or less specific as to structural and methodical features. It is to be understood, however, that the invention is not limited to the specific features shown and described, since the means herein disclosed comprise preferred forms of putting the invention into effect. The invention is, therefore, claimed in any of its forms or modifications within the proper scope of the appended claims appropriately interpreted in accordance with the doctrine of equivalents.

SEQUENCE LISTING

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Asp Asp Thr Ser Cys Arg Leu Phe Asp Ile Arg Ala Asp Arg Glu Leu
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<211> LENGTH: 249
<212> TYPE: PRT
<213> ORGANISM: Aspergillus niger

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Ile Leu Thr Pro Glu Leu Asn Glu Val Val Pro Ala Gly Lys Pro Phe
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Ile Leu Thr Trp Asp Pro Thr Thr Ser Gly Thr Val Ser Leu Val Leu
   50      55        60
Leu Arg Gly Pro Ser Thr Asn Val Val Pro Ile Gin Thr Ile Val Glu
   65      70        75       80
Asp Ile Asp Asn Ser Gly Ser Tyr Ser Trp Thr Pro Ser Thr Thr Leu
   95      100      105       110
Glu Pro Asp Thr Thr His Tyr Gly Ile Leu Leu Val Val Glu Gly Thr
   115      120      125
Gly Gin Tyr Gin Tyr Ser Val Gin Phe Gin Ile Gin Asp Pro Tyr Tyr
   135      140
Ser Ser Ser Ser Val Ala Ala Ala Thr Ser Thr Thr Ala Ala Ala
   150      155      160
Ala Val Ser Ser Asp Ala Ala Thr Ser Thr Thr Thr Ala Ala Ala
   165      170      175
Thr Ser Thr Ile Cys Pro Glu Thr Ala Thr Ala Thr Ala Asp Val Lys
   180      185      190
Pro Thr Ser Val Pro Val Gly Gin Lys Pro Thr Ser Phe Val
   195      200      205
Val Ala Pro Ser Ala Ser Gly Ser Ala Ser Leu Ile Arg Ser Ser Ala
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Thr Pro Ser Gly Thr Pro Ala Ala Ser Ser Ser Val Ser Pro Val
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<212> TYPE: DNA
<213> ORGANISM: Aspergillus niger
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<211> LENGTH: 599
<212> TYPE: PRT
<213> ORGANISM: Aspergillus niger

<400> SEQUENCE: 7

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Arg Ala Asp Gly Val Arg Ala Arg Leu Asp Pro Asn Val Thr Leu Glu
35  40  45
Glu Tyr Met Tyr Trp Ala Lys Ile Glu Arg Gin Leu Glu Glu Glu Glu
50  55  60
Aasn Arg Gin Tyr Val Leu Glu Arg Gly Pro Leu Thr Val Gly Lys Val
65  70  75  80
Ile Gin Aasn Arg Phe Ser Lys Gly Val His His Gly Lys Gly Lys Lys
85  90  95
Gly Ala Gin Aasn Ser Pro Gin Ile Glu Gly Glu Lys Gly Met Val Ala
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Ser Thr Pro Ser Asp Ser Ser Leu Ala Val Thr Asp Glu Glu Trp Arg
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Thr Ala Ala Arg Ala Leu Arg Thr Ala Ser Trp Gly Thr Val Phe Tyr
130 135 140
Leu Ile Thr Thr Asp Val Leu Gly Trp Ala Asn Ala Pro Phe Val Phe
145 150 155

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2083
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Cys Phe Ala Gly Phe Ser Gly Trp Ile Leu Trp Lys Val Phe Leu Glu 165 170 175 180
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Arg Val Phe Gly Ala Trp Ser Arg His Leu Val Asn Ile Gly Gln Ser 205 210 215 220
Leu Gln Leu Leu Met Ser Val Ser Val Leu Val Leu Gly Asn Gly Gln 220 225 230 235 240
Ile Leu Ser Gln Leu Ser Asn Glu Ser Ile Cys Phe Val Ala Cys Met 240 245 250 255 260
Ile Ile His Asp Gly His Arg His Gly Thr Val Glu Ala Phe Gly Pro 265 270 275 280 285
Leu Gln Arg Leu Gly Trp Leu Thr Asn Ala Val Ala Val Trp Leu Asn Ile 290 295 300 305 310
Ala Asp Phe Ile Met Ile Met Val Ala Ala Gly His Phe Gly Ile 315 320 325 330 335
Asp Tyr Gln Ala Val Ile Ser Ser Thr Leu Ile Gln Val Val Glu Pro 340 345 350 355 360 365
Val Lys Val Phe Ala Gly Pro Pro Pro Asp Lys Tyr Gln Ile Gln Ala 370 375 380 385 390 395 400
Thr Gly Phe Ser Gly Gln Phe Thr Gly Val Asp Gln Met Val Tyr Ser 405 410 415 420 425 430 435
Tyr Gly Gly Ala Ile Leu Phe Val Ala Phe Leu Ala Glu Met Arg His 440 445 450 455 460 465 470 475 480 485 490 495 500 505 510
Pro Trp Asp Phe Trp Lys Gly Leu Leu Cys Ala Gln Met Phe Ile Cys 515 520 525 530 535 540 545 550 555 560 565 570 575

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<210> SEQ ID NO 8
<211> LENGTH: 2006
<212> TYPE: DNA
<213> ORGANISM: Aspergillus niger
<400> SEQUENCE: 8

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<210> SEQ ID NO 9
<211> LENGTH: 595
<212> TYPE: PRT
<213> ORGANISM: Aspergillus niger

<400> SEQUENCE: 9

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Trp His His Val Glu Asp Ala Gly Ser Asp His Gin Ile Ser Leu Ser
35    40    45

Ile Ala Leu Ala Arg Lys Asn Leu Asp Gin Leu Glu Ser Lys Leu Lys
50    55    60

Asp Leu Ser Thr Pro Gly Ser Gin Tyr Gly Gin Trp Leu Asp Gin
65    70    75    80

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

Asn Trp Leu Arg Ser Ala Asn Ile Thr His Ile Ser Arg Gin Gly Ser
100   105   110

Leu Val Asn Phe Ala Thr Val Asp Lys Val Asn Lys Leu Leu Asn
115   120   125

Ala Thr Phe Ala Tyr Tyr Gin Ser Gly Ser Gin Arg Leu Arg Thr
130   135   140

Thr Glu Tyr Ser Ile Pro Asp Asp Leu Val Asp Ser Ile Asp Leu Ile
145   150   155   160

Ser Pro Thr Thr Phe Phe Gly Lys Glu Lys Thr Thr Ala Gly Leu Asn
165   170   175

Gln Arg Ala Gin Lys Ile Asp Asn His Val Ala Lys Arg Ser Asn Ser
180   185   190

Ser Ser Cys Ala Asp Leu Ile Thr Leu Ser Cys Leu Lys Glu Met Tyr
195   200   205

Asn Phe Gly Asn Tyr Thr Pro Ser Ala Ser Asp Ser Gly Ser Lys Leu Gly
210   215   220

Phe Gly Ser Phe Leu Asn Gin Ser Ala Ser Tyr Ser Asp Leu Ala Lys
225   230   235   240

Phe Glu Lys Leu Phe Asn Leu Pro Ser Gin Ser Phe Ser Val Glu Leu
245   250   255

Val Asn Gin Gin Gin Gin Val Gin Gin Gin Gin Thr Ala Ser Leu Thr
260   265   270

Glu Ala Asp Leu Asp Val Glu Leu Leu Val Gin Val Ala His Pro Leu
275   280   285

Pro Val Thr Glu Phe Ile Thr Ser Gly Glu Pro Pro Phe Ile Pro Asp
290   295   300

Pro Asp Glu Pro Ser Ala Ala Asp Gin Gin Gin Gin Gin Gin Pro Tyr Leu Gin
305   310   315   320

Tyr Tyr Glu Tyr Leu Leu Ser Lys Pro Gin Ser Ala Leu Pro Gin Val
325   330   335

Ile Ser Asn Ser Tyr Gly Asp Gin Thr Val Pro Glu Tyr Tyr
340   345   350

Ala Lys Arg Val Gin Gin Gin Gin Leu Val Gly Leu Arg Gin Ile
355  Ser Val Leu Glu Ser Ser Gly Asp Glu Gly Ile Gly Ser Gly Cys Arg
360  Thr Thr Asp Gly Thr Asn Arg Thr Glu Phe Asn Pro Ile Phe Pro Ala
365  Thr Cys Pro Tyr Val Thr Ala Val Gly Thr Met Ser Tyr Ala Pro
370  Glu Ile Ala Trp Glu Ala Ser Ser Gly Gly Phe Ser Asn Tyr Phe Glu
375  Arg Ala Trp Phe Glu Lys Glu Ala Val Gin Asn Tyr Leu Ala His His
380  Ile Thr Asn Glu Thr Lys Gin Tyr Ser Gin Phe Ala Asn Phe Ser
385  Gly Arg Gly Phe Pro Asp Val Ala Ala His Ser Phe Glu Pro Ser Tyr
390  465  Glu Val Ile Phe Tyr Gly Ala Arg Tyr Gly Ser Gly Gly Thr Ser Ala
395  490  Ala Cys Pro Leu Phe Ser Ala Leu Val Gly Met Leu Asn Asp Ala Arg
400  500  Leu Arg Ala Gly Lys Ser Thr Leu Gly Phe Leu Asn Pro Leu Leu Tyr
405  510  Ser Lys Gly Tyr Arg Ala Leu Thr Asp Val Thr Gly Gly Gin Ser Ile
410  535  Gly Cys Asn Gly Ile Asp Pro Gin Asn Asp Glu Thr Val Ala Gly Ala
415  555  Glu Ile Ile Pro Trp Ala His Trp Asn Ala Thr Val Gly Trp Asp Pro
420  570  Val Thr Gly Leu Gly Leu Pro Asp Phe Glu Lys Leu Arg Gin Leu Val
425  590  Leu Ser Leu
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Aspergillus niger
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<210> SEQ ID NO 11
<211> LENGTH: 532
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

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Glu Leu Val Gln Ala Val Ser Asp Pro Ser Ser Pro Glu Tyr Gly Lys
35  40  45
Tyr Leu Thr Leu Glu Asn Val Ala Asp Leu Val Arg Pro Ser Pro Leu
50  55  60
Thr Leu His Thr Val Gln Lys Trp Leu Leu Ala Ala Gly Ala Gln Lys
65  70  75  80
Cys His Ser Val Ile Thr Gln Asp Phe Leu Thr Cys Trp Leu Ser Ile
85  90  95
Arg Gln Ala Gln Leu Leu Leu Pro Gly Ala Gln Phe His His Tyr Val
100 105 110
Gly Gly Pro Thr Glu Thr Val His Val Arg Ser Pro His Pro Tyr Gln
115 120 125
Leu Pro Gln Ala Leu Ala Pro His Val Asp Phe Val Gly Gly Leu His
130 135 140
His Phe Pro Pro Thr Ser Ser Leu Arg Gln Arg Pro Glu Pro Gln Val
145 150 155 160
Thr Gly Thr Val Gly Leu His Gly Val His Pro Ser Val Ile Arg
165 170 175
Lys Arg Tyr Asn Leu Thr Ser Gln Asp Val Gly Ser Gly Thr Ser Asn
180 185 190
Asn Ser Gln Ala Cys Ala Gln Phe Leu Glu Gin Tyr Phe His Asp Ser
195 200 205
Asp Leu Ala Gln Phe Met Arg Leu Phe Gly Gly Asn Phe Ala His Gln
210 215 220
Ala Ser Val Ala Arg Val Val Gly Gln Glu Gly Arg Gly Arg Ala Gly
225 230 235 240
Ile Glu Ala Ser Leu Asp Val Gin Tyr Leu Met Ser Ala Gly Ala Asn
245 250 255
Ile Ser Thr Trp Val Tyr Ser Ser Pro Gly Arg His Glu Gly Gin Glu
260 265 270
Pro Phe Leu Gln Trp Leu Met Leu Ser Asn Gin Ser Ala Leu Pro
275 280 285
His Val His Thr Val Ser Tyr Gly Asp Asp Gin Ser Leu Ser Ser
290 295 300
Ala Tyr Ile Gin Arg Val Asn Thr Glu Leu Met Lys Ala Ala Ala Arg
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|       |       |       |       |       |       |       |       |       |       |       |       |       |       |       | 90   |
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| Val   | Ser   | Leu   | Pro   | Thr   | Ala   | Val   | Ser   | Asn   | Gly   | Arg   | Pro   | Arg   | Ala   | Met  | 100  |
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|       |       |       |       |       |       |       |       |       |       |       |       |       |       |       | 110  |
| Arg   | Ala   | Ser   | Tyr   | Tyr   | Gly   | Ser   | Val   | Val   | Met   | Gln   | Ser   | Thr   | Ile   | Lys  | 115  |
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|       |       |       |       |       |       |       |       |       |       |       |       |       |       |       | 140  |
| Asp   | Met   | Leu   | Pro   | Met   | Val   | His   | Pro   | Asn   | Asp   | Leu   | Ala   | Ile   | Gly   | Gly   | Thr  | 145  |
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|       |       |       |       |       |       |       |       |       |       |       |       |       |       |       | 175  |
| Leu   | Gln   | Pro   | Thr   | Leu   | Gln   | Gln   | Val   | Arg   | Lys   | Glu   | Met   | Ala   | Gln   | Met  | 180  |
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| Lys   | Pro   | Leu   | Pro   | Ser   | Ile   | Tyr   | Tyr   | Pro   | Asp   | Phe   | Ile   | Ala   | Ala   | Asn   | Gln | 195  |
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Glu Ser Glu Met Thr Leu Glu His Lys 500 505

<210> SEQ ID NO 15
<211> LENGTH: 505
<212> TYPE: PRT
<213> ORGANISM: Sesamum indicum

<400> SEQUENCE: 15
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Gly Thr Tyr Gln Trp Ile Val Lys Pro Lys Thr Val Lys Tyr Glu Phe 35 40 45
Lys Thr Asp Thr His Val Pro Lys Leu Gly Val Met Leu Val Gly Trp 50 55 60
Gly Gly Asn Asn Gly Ser Thr Leu Thr Gly Val Ile Ala Asn Arg 65 70 75 80
Glu Gly Ile Ser Trp Ala Thr Lys Asp Lys Val Gln Gln Ala Asn Tyr 85 90 95
Phe Gly Ser Leu Thr Gln Ala Ser Ser Ile Arg Val Gly Ser Phe Asn 100 105 110
Gly Glu Glu Ile Tyr Ala Pro Phe Lys Ser Leu Pro Met Val Asn 115 120 125
Pro Asp Asp Val Val Phe Gly Gly Trp Asp Ile Ser Asn Met Asn Leu 130 135 140
 Ala Asp Ala Met Gly Arg Ala Lys Val Leu Asp Ile Asp Leu Gln Lys 145 150 155 160
Gln Leu Arg Pro Tyr Met Glu His Met Val Pro Leu Pro Gly Ile Tyr 165 170 175
Asp Pro Asp Phe Ile Ala Ala Asn Gln Gly Ser Arg Ala Asn Asn Val 180 185 190
Ile Lys Gly Thr Lys Lys Glu Val Gln Val Gln Ile Ile Lys Asp Met 195 200 205
Arg Asp Phe Lys Glu Asn Lys Val Asp Lys Val Val Val Leu Trp 210 215 220
Thr Ala Asn Thr Glu Arg Tyr Ser Asn Val Val Val Gly Leu Asn Asp 225 230 235 240
Thr Ala Glu Ser Leu Met Ala Ser Val Glu Arg Asn Gln Ala Glu Ile 245 250 255
Ser Pro Ser Thr Leu Tyr Ala Ile Ala Cys Val Phe Glu Asn Val Pro 260 265 270
Phe Ile Asn Gly Ser Pro Gln Asn Thr Phe Val Pro Gly Leu Ile Asp 275 280 285
Leu Ala Ile Gln Arg Asn Ser Leu Ile Gly Gly Asp Asp Phe Lys Ser 290 295 300
Gly Gln Thr Lys Met Lys Ser Val Leu Val Asp Phe Leu Val Gly Ala 305 310 315 320
Gly Ile Lys Pro Thr Ser Ile Val Ser Tyr Asn His Leu Gly Asn Asn
Asp Gly Met Ann Leu Ser Ala Pro Glu Thr Phe Arg Ser Lys Glu Ile
325 330 335
Ser Lys Ser Ann Val Val Asp Asp Met Val Ala Ser Ann Gly Ile Leu
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Tyr Glu Pro Gly Glu His Pro Asp His Ile Val Val Ile Lys Tyr Val
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Pro Tyr Val Gly Asp Ser Lys Arg Ala Met Asp Glu Tyr Thr Ser Glu
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420 425 430
Glu Leu Ser Thr Arg Ile Gln Leu Lys Ala Gly Gly Lys Gly Phe
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His Ser Phe His Pro Val Ala Thr Ile Leu Ser Tyr Leu Thr Lys Ala
450 455 460
450 455 460
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<210> SEQ ID NO 16
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<212> TYPE: DNA
<213> ORGANISM: Aspergillus niger
<400> SEQUENCE: 16

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<210> SEQ ID NO 17
<211> LENGTH: 505
<212> TYPE: PRT
<213> ORGANISM: Aspergillus niger
<400> SEQUENCE: 17

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Ser Gly Ala Gly Leu Ile Pro Ile Thr Pro His Glu Thr Asn Gly Gly 50 55 60
Trp Ala Met Ser Pro Asp Gln Glu Cys Lys Pro Gly Gly Tyr Cys Pro 65 70 75 80
Tyr Ala Cys Pro Ala Gly Gln Val Ser Met Gln Trp Asp Pro Glu Ala 85 90 95
Thr Ser Tyr Thr Tyr Pro Met Ser Met Asn Gly Gly Leu Tyr Cys Asp 100 105 110
Glu Asn Gly Glu Ile Gln Lys Pro Phe Pro Asp Arg Pro Tyr Cys Lys 115 120 125
Asp Gly Thr Gly Val Val Ser Ala Lys Asn Lys Cys Lys Gln Val 130 135 140
Ser Phe Cys Gln Thr Val Leu Pro Gly Asn Glu Ala Met Pro Ile Pro 145 150 155 160
Thr Leu Val Glu Pro Ala Thr Leu Ala Val Pro Asp Leu Ser Tyr 165 170 175
Trp Cys Glu Thr Ala Ala His Phe Tyr Ile Asn Pro Pro Gly Tyr Asn 180 185 190
Thr Lys Thr Ala Cys Val Trp Gly Thr Ser Glu Asn Pro Tyr Gly Asn
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<210> SEQ ID NO 18
<211> LENGTH : 1904
<212> TYPE : DNA
<213> ORGANISM : Aspergillus niger
<400> SEQUENCE : 18

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<210> SEQ ID NO 19
<211> LENGTH: 460
<212> TYPE: PRT
<213> ORGANISM: Aspergillus niger

<400> SEQUENCE: 19

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Val Ser Glu Gly Lys Tyr Thr Ile Gly Leu Gly Gln Thr Lys Met Ser
35  40  45

Phe Cys Asp Arg Arg Ala Gly Ile Tyr Ser Ile Ala Leu Thr Thr Phe
50  55  60

Ser Ser Leu Leu Arg Lys Tyr Asn Ile Asp Pro Asn Ser Ile Gly Arg
65  70  75  80

Leu Glu Val Gly Thr Glu Thr Leu Leu Asp Ser Lys Ser Val Lys
85  90  95

Ser Val Leu Met Gln Leu Ala Pro His Gly Asn Thr Asn Val Glu

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<212> TYPE: PRT
<213> ORGANISM: Aspergillus niger
<400> SEQUENCE: 20

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<td>Asn Thr Glu Thr Leu Tyr Pro Gly Thr Tyr Tyr Thr Leu Thr Glu Val</td>
</tr>
<tr>
<td></td>
<td>435</td>
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<tr>
<td>--------</td>
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<tr>
<td>Asp</td>
<td>450</td>
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<tr>
<td>Asp</td>
<td></td>
</tr>
<tr>
<td>Met</td>
<td></td>
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<210> SEQ ID NO 21
<211> LENGTH: 454
<212> TYPE: PRT
<213> ORGANISM: Neurospora crassa

<400> SEQUENCE: 21

Met Ala Thr Arg Pro Gln Asn Ile Gly Ile Lys Ala Ile Glu Ile Tyr 1 5 10 15
Phe Pro Ser Gln Tyr Val Glu Gln Ser Glu Leu Glu Lys Phe Asp Gly 20 25 30
Val Ser Thr Gly Lys Tyr Thr Ile Gly Leu Gly Gin Thr Lys Met Ala 35 40 45
Phe Cys Asp Arg Asp Gin Ile Tyr Ser Leu Ala Leu Thr Ala Val 50 55 60
Ser Arg Leu Leu Lys Asn Tyr Glu Ile Asp Thr Asn Thr Ile Gly Arg 65 70 75 80
Leu Glu Val Gly Thr Leu Thr Leu Asp Lys Ser Lys Ser Val Lys 85 90 95
Ser Val Leu Met Gin Leu Phe Gly Glu Asn Thr Asn Ile Glu Gly Val 100 105 110
Asp Thr Ile Asn Ala Cys Tyr Gly Gly Thr Asn Ala Phe Phe Asn Ser 115 120 125
Val Asn Trp Ile Glu Ser Ser Ala Trp Asp Gly Arg Asp Ala Ile Val 130 135 140
Val Ala Gly Asp Ile Ala Leu Tyr Ala Lys Gin Asn Ala Arg Pro Thr 145 150 155 160
Gly Gly Ala Gly Cys Val Ala Met Leu Val Gly Pro Asn Ala Pro Ile 165 170 175
 Ala Val Glu Pro Gly Leu Arg Gly Ser Tyr Met Ala His Ala Tyr Asp 180 185 190
Phe Tyr Lys Pro Asp Leu Thr Ser Glu Tyr Pro Tyr Val Asp Gly His 195 200 205
Tyr Ser Val Asn Cys Tyr Thr Glu Ala Leu Asp Gly Ala Tyr Arg Ala 210 215 220
Tyr Asn Gin Arg Glu Lys Leu Thr Asp Gin Val Asn Gin His Ser 225 230 235 240
Glu Asp Ser Thr Lys Thr Pro Leu Asp Arg Phe Asp Tyr Leu Ala Phe 245 250 255
His Ala Pro Thr Cys Lys Leu Val Gin Lys Ser Tyr Ala Arg Leu Leu 260 265 270
Tyr His Asp Tyr Leu Ala Asn Pro Glu Ser Pro Val Phe Ala Asp Val 275 280 285
Pro Pro Glu Val Arg Asp Met Asp Tyr Lys Ser Leu Thr Asp Lys 290 295 300
Val Val Glu Lys Thr Phe Met Thr Leu Thr Lys Arg Phe Gin Glu 305 310 315 320
Arg Val Asn Pro Ala Ile Gin Val Pro Thr Leu Cys Gin Asn Met Tyr 325 330 335
Cys Gly Ser Val Thr Gly Gly Leu Ala Ser Ile Ile Gly His Val Asp 340 345 350
Ser Ala Gln Leu Glu Gly Lys Arg Ile Gly Leu Phe Ser Tyr Gly Ser
355
360
365
Gly Leu Ala Ala Ser Phe Cys Ser Ser Phe Arg Val Thr Gly Ser Thr Glu
370
375
380
Lys Leu Ala Lys Thr Leu Asn Leu Pro Ala Arg Leu Ala Ala Arg Arg
385
390
395
400
Ala Val Pro Pro Glu Ser Tyr Asp Ala Met Cys Asp Leu Arg Lys Gln
405
410
415
Ala His Leu Gln Lys Asn Tyr Thr Pro Lys Gly Glu Val Ser Thr Leu
420
425
430
Glu Pro Gly Thr Tyr Thr Leu Glu Asn Val Asp Met Phe Lys Arg
435
440
445
Thr Tyr Ser Ile Lys Ala
450

<210> SEQ ID NO 22
<211> LENGTH: 1498
<212> TYPE: DNA
<213> ORGANISM: Aspergillus niger
<400> SEQUENCE: 22

agcataaatt cttcctccct tgaatctcaac tacacctctct taagaaagtctg ctgctctgac 60
cctcttctg cttcatcttt tttctgttaa tactataaac tacatacaac tcaactctct tctattcttt 120
caatagag ttcacaggaac ctctttctgc ccaatcgtctg ccgctcagcc 180
ggcatggcc gggcagaacg cagtcgctcc caaagctgt ggcagcagcag gatgctccct 240
cctcttcggt gggttcctcct ccaagcctcct ccctttgtctct cctcctccgg 300
cgccgcgcc ggggagccag gctctgtgcct ccaaaagctgt caggggcagg cctccaggt 360
gagctgtgag gcgcttccttc agcctctccact gcctgctcttc gctgcttctgc 420
agcctctctgt gcgctcttaga ggcgctcagt ccagatcagg cttcctcttc ccaaacgcctc 480
cggccgagagt gccgctcagt ctggctcagag ctcctggcag gcggcctcctc cttctgtctc 540
tctctgtcag gcgcttccttc ccctgtcagat ccctgccgctc tctttcttctc 600
ttcgtctgag caggggagcc gcgtctacttc tttctctcttt gggcagcgcc gggccacag 660
cattgctcttc gcgcttccttc gcagttctttc gctgctctgag ccctgccgctc 720
gtctctgtcag gcgcttctcc cctttccttc ggtcttcttc gcgcagcagc ggcgctccag 780
ggcagcagc gcgtctctcttc ccagaggcag cagcctcttc ggcgctccag ggcgctcctc 840
tctccctttg tcaacgacag ccgtaaggctc tctgctgctc tctgctgctc gaacgctcag 900
tccatcaggag tgaacagcag gcgcttcttc gcagttctttc gcctgcttcttc 960
caggtctcttg cctcctcttc ctggccgctc aacgctgctc tctctcttct tctgctgctc 1020
ggcgagcag ccctctcttc cgggtctcttc gcgcagctccg ctgcctctctt tctctcttct 1080
gcgcttcttc ccgctccgctc tcggctcttc gcgcagctccg ctgcctctctt 1140
gcgcctcag ccgctccgctc tcggctcttc gcgcagctccg ctgcctctctt 1200
gcgctcagcc gcggccgctc tcggctcttc gcgcagctccg ctgcctctctt 1260
tctctctcttc tctcctcttc ccgctccgctc tcggctcttc gcgcagctccg ctgcctctctt 1320
tctcctctccattgctc cctcctcttc ctggcagag ccagctccgctc tcggctcttc gcgcagctccg ctgcctctctt 1380
tccgagcttc gcggccgctc tcggctcttc gcgcagctccg ctgcctctctt 1440
tccgagcttc gcggccgctc tcggctcttc gcgcagctccg ctgcctctctt 1498
<210> SEQ ID NO 23
<211> LENGTH: 404
<212> TYPE: PRT
<213> ORGANISM: Aspergillus niger

<400> SEQUENCE: 23

Met Lys Phe Thr Gly Ile Ala Phe Ala Gly Leu Ile Gly Tyr Ala Ala
  1      5     10      15
Ala Leu Pro Ala Met Gly Ala Gin Gin Asp Ser Ala Pro Gin Gly Val
 20     25
Gln Ala Thr Gly Ala Pro Ser Phe Gin Gly Ala Pro Ser Gly Ser
  30     35     40     45
Pro Leu Pro Leu Pro Ser Gly Ala Pro Gin Gly Gin Gly Phe Gly Gly
  50     55     60
Gln Gly Phe Gly Asn Ser Asn Gly Gin Gin Gin Ala Pro Thr Val Ser
  65     70     75     80
Leu Gly Asp Ala Pro Gin Pro Pro Thr Gly Ser Ala Ala Pro Ala
  95     100    105     95
Pro Ser Gly Ala Pro Arg Gly His Lys Arg Arg Gin Leu Gin Leu Ile Pro
 110
Ala Ser Val Ser Asn Val Pro Ala Pro Thr Gly Ser Ala Ala Ala Gly
 115     120    125
Gly Asp Phe Gly Gly Ala Pro Ser Gly Pro Ala Pro Ser Gly Ala Ala
 130     135    140
Pro Ser Gly Val Ala Gly Asp Gly Pro Ser Pro Ser Gly Ser Phe
 145     150    155    160
Gly Gly Gin Gly Gly Gin Ser Gly Ser Phe Gly Gly Asn Gly Ala Ala
 165     170    175
Pro Ser Gly Ile Ala Gly Gly Ala Gly Pro Ser Thr Ser Gly Ser Phe
 180     185    190
Gly Gly Ala Ala Pro Pro Val Leu Leu Val Ala Met Ala Pro Leu Pro
 195     200    205
Pro Ala Leu Leu Ala Ala Ser Arg Val Ser Arg Ala Arg Ala Ala Ser
 210     215    220
Ala Ala Arg Thr Pro Ser Pro Arg Ala Ser Pro Arg Thr Pro Ser Leu
 225     230    235    240
Arg Ala Leu Ser Pro Arg Thr Pro Gly Leu Arg Ala Leu Ser Arg
 245     250    255
Thr Pro Ser Pro Arg Asp Leu Thr Leu Arg Asp Leu Arg Ala Leu Ser
 260     265    270
Ser Arg Ala Pro Pro Leu Ser Arg Ala Leu Ala Leu Ala Leu Ser Val
 275     280    285
Val Thr Val Leu Leu Pro Pro Val Leu Val Ala Thr Ala Pro Leu
 290     295    300
Leu Pro Ala Leu Ser Ala Val Leu Leu Pro Pro Val Leu Leu Ala Ala
 305     310    315    320
Thr Val Pro Leu Pro Leu Ala Pro Ser Ala Val Thr Ala Leu Leu Pro
 325     330    335
Leu Thr Ser Leu Val Glu Thr Ala Pro Leu Leu Pro Ala Pro Ser Val
 340     345    350
Val Thr Val Leu Leu Leu Val Leu Pro Val Leu Leu Pro Leu Pro
 355     360    365
Arg Ala Pro Pro Pro Pro Leu Pro Arg Val Leu Thr Lys Ser Met
 370     375    380

-continued
Arg Lys Ser Trp Thr Ser Ile Asp Asn Lys His Leu Pro Tyr His Leu
385 390 395 400
Thr Leu Met Gln

<210> SEQ ID NO 24
<211> LENGTH: 763
<212> TYPE: DNA
<213> ORGANISM: Aspergillus niger

<400> SEQUENCE: 24

acacaaagca cactcctac atcctctac gttttttcttt cactcctta cttctctac 60
ttcacatat tcagcatgca gtggagacac tttctgtgcc ctcgtgtgct ctagcaggtct 120
agcttgctgtg ctgcctggtgg caccaacgcg aagagagaa gctggacacaa tggacccctg 180
ttgctactag gacagaactc ttcgctttac ccacctgttt atgggctca gtagtggtctt 240
tctacatttc cccagactgc ggagacaccc ggcggagacc tgcacccaat gttcttggtgat 300
tgcctcctca tcacagtata gttggtgatt gtcacagcag cgttatgtaga tggagacccgt 360
gcagagatcc tctatattcg acgacagata aacaacctgtt ttgcgctgtgct gctttttgcc 420
cagagttaag gggtgatacg cgtgtcagag ggttttgccct ttttgcacat gcagctgtgc 480
tataacacgg atacccagatg ggaagcacac tttcggcgct ctagacagagt ctggagagat 540
gttctacaac ggctgtgggt gcagacgtct tcgcaasttg caggggaaac ccctctgcgctc 600
gtgggtgaaag ctgccccaggt ctcagacatga aagagacagc gactccaggga ggtgtgacat 660
ggggtgtgtgg gttggtgctc gcagcagatt gttgcctgtgc gctaatatat 720
ataatgctca ctgctttata tttgacaaaa aaaaaaaaaa aaa 763

<210> SEQ ID NO 25
<211> LENGTH: 164
<212> TYPE: PRO
<213> ORGANISM: Aspergillus niger

<400> SEQUENCE: 25

Met Gln Trp Thr Asn Phe Leu Cys Pro Leu Ile Ala Met Gln Ala Ser
1  5  10 15
Leu Ser Ala Ala Trp Gly Thr His Val Lys Arg Gly Ser Glu Thr Asn
20 25 30
Ala Thr Leu Phe Ala Tyr Gly Gln Asn Ser Ser Ala Tyr Pro Ile Ala
35 40 45
Tyr Gly Leu Ser Asp Gly Leu Tyr Ile Ala Gln Asp Pro Glu Asn
50 55 60
Thr Ala Ala Asp Leu Thr Pro Met Ser Trp Asp Leu Pro Ser Ile Thr
65 70 75 80
Asp Glu Cys Trp Ile Val Asn Gly Thr Phe Met Asn Gly Thr Arg Ala
85 90 95
Gly Ser Leu Tyr Ile Arg Pro Asp Ser Asn Asn Cys Leu Gly Val Leu
100 105 110
Pro Phe Ala Gln Ala Lys Gly Val Asn Gly Val Thr Gly Phe Gly
115 120 125
Leu Phe Ala Ser Gln Leu Val Tyr Asn Asn Thr Glu Leu Glu Ala
130 135 140
Gln Phe Trp Ala Ser Lys Thr Asp Thr Gln Asp Val Tyr Lys Leu Val
145 150 155 160
Trp Val Glu Asp Ser Ser Gln Ile Ala Ser Glu Ser Phe Pro Val Val
Val Lys Ala Ser Glu Asp Ser Thr
180

<210> SEQ ID NO 26
<211> LENGTH: 641
<212> TYPE: DNA
<213> ORGANISM: Aspergillus niger

<400> SEQUENCE: 26

acctcaacatt tttcatatctg tcttcggtac ctagattctc tcattatatc ttcgcctgtg 60
tcttcttttt cttgccaaga ttttagccat cttacaacc gcagagaaaa tcattcccat 120
cctatcacat cacaatgctc gcgtggctgc ctcgctgtcc ccagtttaac ggtgaccggc 180
cggagaggg tcactcacaat gaaagagtt ccctgcagcc cagttccgac cgaacccagg 240
cgtctgaaggg tggagaagggct gtctacacgc tttgagtgag cagctatcct ctcgctcag 300
tggagctcgtg gcagctgggg gcggaaatca tcactgaacc cgacttgtcc aaccttaccc 360
gttacgagtt gcagcgccgct cttgacacca tttgacgttt tggagcaggg atcgagcggc 420
gctgtgtcgag gcagacgtaga gttnaggttc gcggctggaa tatactgcga agatagtttg 480
attgcgtttg aggctgttcc ggcttgccgc tggagcaagtt attgatatgg acatggaaccat 540
ggtatagtggt tgtatagttg tgaagctgtca cattatctca ctggatgatgc ttcgatgaag 600
ttacggtgac gatctcttct ttcagaaaaa aaaaaaaaaa a 641

<210> SEQ ID NO 27
<211> LENGTH: 101
<212> TYPE: PRT
<213> ORGANISM: Aspergillus niger

<400> SEQUENCE: 27

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

<210> SEQ ID NO 28
<211> LENGTH: 1243
<212> TYPE: DNA
<213> ORGANISM: Aspergillus niger

<400> SEQUENCE: 28

cggtcgggag aagaggggaca ctgacatgga ctagagagtt agaaagagtc ttctttctcc 60
acccctccag ccctctctct cttgcaacct gcggctactg gttggaccca ttctttctct 120
cctggaacat atgcgtgctgg tcagaggtgct gcactaccca ctctgtccga gacactctgg 180
agagaacgga cttctctcata cttcagatat atacatacag atacattcctc ttcgaacaaa 240
acccgaacaga attcgaagaa cacatacaca atgtgtctct tcaagtctct tcctgacgcc 300
acccaccttg gcacccggctg tcctgccacg cctctagctg gcacccggcctt gcggcgagcc 360
aagacacgtt ccacccacgtt gcacctcggaa ggaaaccttc gcctccaaag gcctggtgcc 420
tacaactctg ctcctcagctg ttcaaaatgtg acctcgggtct ctctccgacca cggtaaccgc 480
tctggtggtct cagctgatctc cagttgcgcc gccgcccccc tccctaatga cctgtaatac 540
gtgcctcatt gcgtggggcag caaagatgtt gcaggtcgtgt tcagcgcctat cggagactgcc 600
cctgacacagcg tgaacatta ctaaagagga ttcatagccag tttaacttgcc 660
ctgatgactg ctcctcagggc gcgcagctcc taacatagat acctcactgc ttactcttgc 720
aaggtcaagcg tgcggtcacc gcactgcgcc agtagaacca cggaaaccgga gggcttcagc 780
tgtagatggt ctcctgcttc gcgaagcagc gcttgtgcagct cggctatcacc 840
tgtagctgcct cctgcagcgctg cttcttgctgc gcaggtgctgc cggagctgcg 900
gacgaaacag gatttggaac gctcctgggtgc acaagatgctgc ccccccaagag gcagggg 960
gccggcgcct gcgcaggtcag aggcgggaga tcctctggcgg aggtttggccc gttggtggggc 1020
agcacaggtcc ggtggtggac gtatccgtat cacagtggtt cagtgtccag 1080
gggaggagatt gcacacggct tcagcagagtc gacatctgctc gcagagcctcc 1140
gactacatta gactctgttt atcctggcaacct tttatcacgtt gattacgctgctc 1200
tttatcctat tccatcctac cccatctaga ggggagagac gacgacactc 1260
ccacttattc ccacccactt tccccctcca aatattccac cttcgaattg aatcgaattc 1320
aatacataaa aaaaaaaaaa aaaa 1343

<210> SEQ ID NO 29
<211> LENGTH: 263
<212> TYPE: PRT
<213> ORGANISM: Aspergillus niger
<220> FEATURE:
    <221> NAME/KEY: MISC_FEATURE
    <223> OTHER INFORMATION: gap in homologous sequence
<400> SEQUENCE: 29

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

<210> SEQ ID NO 30
<211> LENGTH: 22
<212> TYPE: PRT
<213> ORGANISM: Aspergillus niger

<400> SEQUENCE: 30
Lys Arg Arg Lys Asp Glu Leu Ala Asp Thr Thr Leu Arg Gin Val Ala
1 5 10 15
Gln Asn Gin Thr Glu Thr
20

<210> SEQ ID NO 31
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Aspergillus niger

<400> SEQUENCE: 31
Leu Gly Asp Val Met Ser Ile Ser Ile Asn Pro Thr Asn Gin Asn Val
1 5 10 15

<210> SEQ ID NO 32
<211> LENGTH: 29
<212> TYPE: PRT
<213> ORGANISM: Aspergillus niger

<400> SEQUENCE: 32
Ser Cys Arg Leu Phe Asp Ile Arg Ala Asp Arg Glu Leu Asn Thr Tyr
1 5 10 15
Gln Ser Asp Gin Ile Leu Cys Gly Ile Thr Ser Val Ala
20 25

<210> SEQ ID NO 33
<211> LENGTH: 1221
<212> TYPE: DNA
<213> ORGANISM: Aspergillus niger

<400> SEQUENCE: 33
taccatacgcctttcggcatacgacatcggctctccccacaacaactcaccattaga 60
catacaccatactgctctttaccactcggagtacgttcgttaagaacctctccacgcggcaaa 120
ggatacatactcgacctccgctgctaccctcaggaccgcagaacgctcagaacgacatcacc 180
ggataaggagggatcactcctgccatacggctctccgggtaatgtggagtcgcttcggtcgg 240
ggtgaggcgc acgtctagtg acctacacat ccgaaggg gctactcttcc atctttgctct 300
ccgctctgct ggtggtatgc agatatcctgt caagaccctg accggaaga caacccacct 360
tggagtggag tcctgctaga cactcggcaca tggagaagcc aagattcagg acaagaggg 420
cattcaccgg gacaccaggc gtctgtacctc cgtctggaaag agctgaggg agtgccgatac 480
cgctgtgac tacaccatctt aaagagatatc cacccctcag cctcggctctc ctctgtgctgt 540
tgtgtatgacg atccttggcag acactctcag gggaagagcg aaccaattgg aagttgatac 600
ttttaccacca aatgataacg ttaaagacca gattcaagac aagagagcga tcccccccga 660
ccagcaacct tgtatctccg ctggtaagca gttggaggg atgccgtact tggcgcaca 720
caactaccc gaaagaagcc cttcttcacct tggctctctct cgtcttgggt gtatgcaaat 780
ctgttgagga actcttaccc cgaacagcat taccgtggag gtggaggcgt cggatacct 840
tgataaacct aacataaaag ttcgataaaat ggagggcatt tccccgggacc agcagcgct 900
catctctctg ggtaagcaagt tggaaagatgg aagttcagcct cagcggtaga cagacttcga 960
ggagacact cttccaccttg tgtcgcctgtc cggctgcccga aactatgcccc tttttttgt 1020
cctttctctt tagcaagcct catctacccg tggatccgtt gtgtggcggt ggtgagcggt 1080
tttttcatcg tttttttag tgcgtataaat tggccataac tttggtctcag catcttcctc 1140
ggggcttgc tgcattcttt taccctggaa tcaattcataa aacatacattc ccacgtgat 1200
ctaaaaaaa aaaaaaaaaac t 1221

<210> SEQ ID NO 34
<211> LENGTH: 236
<212> TYPE: PRT
<213> ORGANISM: Aspergillus niger
<400> SEQUENCE: 34

Val Leu Arg Leu Arg Gly Gly Met Gln Ile Phe Val Lys Thr Leu Thr
1    5    10    15
Gly Lys Thr Ile Thr Leu Glu Val Glu Ser Ser Asp Thr Ile Asp Asn
20   25   30
Val Lys Thr Lys Ile Gln Asp Gly Lys Ile Pro Pro Asp Gln Gln
35   40   45
Arg Leu Ile Phe Ala Gly Lys Gln Leu Glu Asp Gly Arg Thr Leu Ser
50   55   60
Asp Tyr Asn Ile Gln Lys Glu Ser Thr Leu His Leu Val Leu Arg Leu
65   70   75   80
Arg Gly Gly Met Gln Ile Phe Val Lys Thr Thr Gly Lys Thr Ile
85   90   95
Thr Leu Glu Val Glu Ser Ser Asp Thr Ile Asp Asn Val Lys Thr Lys
100  105  110
Ile Gln Asp Lys Gly Gly Ile Pro Pro Asp Gln Gln Arg Leu Ile Phe
115  120  125
Ala Gly Lys Gln Leu Glu Asp Gly Arg Thr Leu Ser Asp Tyr Asn Ile
130  135  140
Gln Lys Glu Ser Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly Met
145  150  155  160
Gln Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu Val
165  170  175
Glu Ser Ser Asp Thr Ile Asp Asn Val Lys Thr Lys Ile Gln Asp Lys
180  185  190
-continued

Glu Gly Ile Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys Gln
 195  200  205
Leu Glu Asp Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu Ser
 210  215  220
Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly Asn
 225  230  235

<210> SEQ ID NO 35
<211> LENGTH: 235
<212> TYPE: PRT
<213> ORGANISM: Aspergillus niger

<400> SEQUENCE: 35
Val Leu Arg His Ala Asn Asn Leu Ala Val Val Lys Thr Leu Thr Gly
  1    5    10    15
Lys Thr Ile Thr Leu Glu Val Glu Ser Ser Asp Thr Ile Asp Asn Val
 20    25    30
Lys Thr Lys Ile Gln Asp Lys Glu Gly Ile Pro Pro Asp Gin Gin Gln Arg
 35    40    45
Leu Ile Phe Ala Gly Lys Gin Leu Glu Asp Gly Arg Thr Leu Ser Asp
 50    55    60
Tyr Asn Ile Gln Lys Glu Ser Thr Leu His Leu Val Leu Arg Leu Arg
 65    70    75    80
Gly Gly Met Gin Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr
 85    90    95
Leu Glu Val Gin Gin Ser Ser Asp Thr Ile Asp Asn Val Lys Ser Lys Ile
100   105   110
Gln Asp Lys Glu Gly Ile Pro Pro Asp Gin Gin Gln Arg Leu Ile Phe Ala
115   120   125
Gly Lys Gin Leu Glu Asp Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gin
130   135   140
Lys Glu Ser Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly Met Gin
145   150   155   160
Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu Val Glu
165   170   175
Ser Ser Asp Thr Ile Asp Asn Val Lys Thr Lys Ile Gin Asp Lys Glu
180   185   190
Gly Ile Pro Pro Asp Gin Gin Gin Arg Leu Ile Phe Ally Gly Lys Gin Leu
195   200   205
Glu Asp Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gin Lys Glu Ser Thr
210   215   220
Leu His Leu Val Leu Arg Leu Arg Gly Gly Asn
225   230   235

<210> SEQ ID NO 36
<211> LENGTH: 404
<212> TYPE: DNA
<213> ORGANISM: Aspergillus niger

<400> SEQUENCE: 36
tcgagcggcc gccggcagg tacctccctt atgctctgg atgaagacgt ggttactgcc 60
tatatgtgg aagttccaca ctcgtcctac gtgacagtg ccgttgtaaa catotaccc 120
tgacacca cttctccag cttctcgttt gttctcggag atgtcgagct ggccacgttc 180
tccgccgatc tgaatcatt ttcgcaggtt ggcccaccac ccacacccg cagggcttg 240
tgtttgcgg gcaatcattt ccacggggact acctcctggc agattctggg cgtatatccc 300
1. A method of promoting a morphology in a fungus comprising:
providing a recombinant polynucleotide comprising an antisense oriented sequence that is complementary to a gene coding region that is differentially expressed in a native fungus exhibiting a pellet morphology relative to said native fungus exhibiting a filament morphology wherein the complementary sequence is complementary to an entirety of SEQ ID NO: 4;
translating Aspergillus niger;
transcribing the antisense oriented sequence to produce a transcription product of sufficient length to hybridize to a gene coding sequence transcription product to block translation; and
suppressing expression of the gene coding region utilizing transcription products produced by expression of the recombinant polynucleotide, the suppression promoting a pellet morphology capable of being assumed by the fungi in its native form.

2. A method of enhancing a bioprocess utilizing a fungus, comprising:
producing a transformed fungus by transforming Aspergillus niger with a recombinant polynucleotide molecule comprising a polynucleotide sequence complementary to the entirety of SEQ ID NO: 4, linked operably to a promoter, the polynucleotide sequence being in antisense orientation;
transcribing the polynucleotide sequence to produce polynucleotide transcripts; and
hybridizing the transcripts to mRNA to suppress gene expression and promote pellet morphology, the pellet morphology enhancing a bioprocess relative to the bioprocess utilizing a filamentous morphology of the transformed fungus; the bioprocess comprising production of citric acid.
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 5, line 52 – Replace “member any of” with --member of any of--.

Column 10, line 44 – Replace “database” with --database--.

Column 10, line 56 – Replace “Balu-4.” with --Balu-4--.

Column 11, line 31 – Replace “under stood” with --understood--.

Column 12, line 49 – Replace “2729” with --27, 29--.

Column 14, line 20 – Replace “amount of amount of” with --amount of--.

Column 14, line 41 – Replace “(1998)” with --(1989)--.

Column 14, line 52 – Replace “to one the” with --to one of the--.

Signed and Sealed this
Seventeenth Day of March, 2009

John Doll
Acting Director of the United States Patent and Trademark Office