Yves Brun
System Biology/Microbiology Faculty Search,
Department of Biology
Indiana University
Jordan Hall 142, 1001 E 3rd Street
Bloomington, IN 47405-7005

September 15, 2005

Dear Dr. Brun,

It is my great pleasure to submit my application for the faculty position in the Department of Biology.

Since 1999, I have been an Assistant Professor in the Department of Medical Biochemistry and Genetics, TAMUSHSC/COM, leading a productive lab. In the past six years, I have developed three active research areas. My lab published 11 papers and I am the senior author for 7 of them. I am the PI on four extramurally funded grants with over $2,000,000 of total direct and indirect costs. I am also the inventor of the TAMUS 2032 technology which is a potent in animal growth promotion and immunomodulation with an estimated annual market potential of $500 mil. US and PCT patent applications are filed to protect the intellectual property. Major drug companies are actively evaluating the technology for licensing.

Recently a lot of things have changed in my current institution. We lost 25% of our faculty, and most significantly, my former department head Dr. Hagan Bayley who recruited me left for Oxford University. I have decided to move my lab to find a better environment and elevate my research to the next level.

I look forward to hearing from you to discuss my qualifications.

Sincerely,

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Research Areas and Future Plans

Yi Wei Jiang
9/2005

Area 1: *Ty1* transcriptional pseudo-cosuppression in *S. cerevisiae*

To control molecular parasites (such as viruses and transposons) and maintain genome integrity, eukaryotic organisms have evolved mechanisms of cosuppression (i.e. RNA interference) that silence gene expression in a high copy number-dependent and homology-dependent fashion. Cosuppression can occur at the transcriptional and/or posttranscriptional levels. *S. cerevisiae* lab strains contain about 30 copies of the *Ty1* retrotransposons, and 5-20% of total yeast mRNA pool in vivo is made of *Ty1* mRNA molecules that are poorly translated. I discovered that *Ty1* transcription could be silenced in response to a high *Ty1* copy number. This phenomenon appeared to fit the classic definition of cosuppression. However, the phenomenon is ***homology-independent***, as over-expression of non-translatable mRNA with no *Ty1* homology can also silence *Ty1* transcription. We have renamed the phenomenon *Ty1* transcriptional pseudo-cosuppression (TPCS). TPCS therefore represents ***a novel host genome defense strategy***. Our current research is focusing on the following three key aspects of *Ty1* TPCS.

First, how do yeast cells detect non-translatable mRNA? Our current working model is as follows. The nuclear cap binding protein complex (CBP) is required for the pioneer round of translation in the cytoplasma, and over-expression of non-translatable mRNA may cause CBP to be trapped in the cytoplasma and depletion of CBP in the nucleus. CBP is also required in the nucleus for normal pre-rRNA processing and pre-mRNA splicing of ribosome proteins. In other words, over-expression of non-translatable mRNA may result in a block in ribosome synthesis and a subsequent translation block.

Second, how is *Ty1* transcription silenced? We have found that a well-known transcriptional regulator Gcn4 binds to *Ty1* and represses its transcription.

Third, how is the signal of a translation block transmitted to the *Ty1* transcriptional repressor Gcn4? The conserved general translational regulator Gcn2 activates the Gcn4 translation in response to translation stress caused by amino acid starvation. Gcn2 is also required for *Ty1* TPCS. Gcn2 may also be activated by translation stress due to a block in ribosome biosynthesis.

Funding

NIH R01GM65320, $900,000 direct cost (01/2004-12/2008).
Cossupression of *Ty1* Retrotransposon in *S. cerevisiae*

Publications

Transcriptional Cosuppression of Yeast *Ty1* Retrotransposons
Jiang Y.W*. Genes & Development 16: 467-478 (2002).

Glc7/Reg1-dependent Glucose Repression of *Ty1* Transcription and Transposition in *S. cerevisiae*
Xiaofeng Wu and Yi Wei Jiang* (submitted, 2005)

Gcn4-mediated *Ty1* Transcriptional Pseudo-Cosuppression.
Xiaofeng Wu and Yi Wei Jiang* (submitted, 2005)

The Glc7 Phosphatase Inhibits Ty1 Transcriptional Pseudo-cosuppression by Opposing Gcn2-mediated Gcn4 Translational Activation in *S. cerevisiae*
Xiaofeng Wu and Yi Wei Jiang* (submitted, 2005)

Inhibition of the Filamentous MAPK Pathway by ATP/CPF: A Gcn4-independent Mechanism for *Ty1* Transcriptional Pseudo-cosuppression
Xiaofeng Wu and Yi Wei Jiang* (in preparation, 2005)

Future Plan

The top priority of this research area is to publish the large number of results we have obtained to anticipate the renewal of R01GM65320 in 2008. There are three new specific aims that I plan to propose in the renewal. First, to understand the mechanism for Gcn4 (a known transcriptional activator) to function as the key transcriptional repressor in Ty1 TPCS; Second, to understand how Gcn2 is activated in response to CBP depletion in the nucleus; Third, to learn other consequences of CBP depletion.

Area 2: Slowed DNA synthesis-induced filamentous differentiation of *S. cerevisiae*

A key question in eukaryotic ***differentiation*** is whether there are common regulators or biochemical events that are required for diverse types of differentiation or whether there is a core mechanism for differentiation. The unicellular model organism *S. cerevisiae* undergoes filamentous differentiation in response to environmental cues. Since conserved cell cycle regulators, the mitotic cyclin-dependent kinase Clb2/Cdc28 and its inhibitor Swe1, were found to be involved in both nitrogen starvation- and short chain alcohol-induced filamentous differentiation, they were identified as components of the core mechanism for filamentous differentiation. We have discovered that slowed DNA synthesis also induces yeast filamentous differentiation through conserved ***checkpoint*** proteins Mec1 and Rad53. The mechanism for Rad53 activation in filamentation is distinct from the classic phosphorylation by Mec1 in response to DNA damage or replication block. Swe1 and Clb2 are also involved in this form of differentiation, and the core status of Swe1/Clb2/Cdc28 in the mechanism of filamentous differentiation has therefore been confirmed. Slowed DNA synthesis also induces differentiation in mammalian cancer cells, and such stimulus conservation may indicate that the core mechanism for yeast filamentous differentiation is conserved in mammalian differentiation. Therefore, yeast filamentous differentiation may be an excellent model for ***cancer*** development and therapeutics. The human homologues of *MEC1* and *RAD53* (ATM/ATR and CHK2 respectively) are indeed known ***tumor suppressor*** genes. Our studies of yeast differentiation may help shed light on human cancer development and the discovery of novel anticancer drugs. In addition, filamentous growth is key to virulence of pathogenic fungi, another human health problem.

Funding

NIH R01GM070568 (application to be resubmitted),
$200,000 annual direct cost for five years,
Slowed DNA Synthesis-induced Filamentous Growth in Yeast.

Publications

Induction of *S. cerevisiae* Filamentous Differentiation by Slowed DNA Synthesis Involves Mec1, Rad53 and Swe1 Checkpoint Proteins.
Jiang Y.W*. and Kang C. M. Mol. Biol. Cell 14: 5116-24 (2003)

Genome-wide Survey of Genes Required for Filamentous Differentiation of *S. cerevisiae.*
Kang C. M. and Jiang Y.W*. Yeast 22(2): 79-90 (2005).

Integration of Upstream Signals at Cdc42 in Filamentous Differentiation of *S. cerevisiae*
Xiaofeng Wu and Yi Wei Jiang*. Yeast (In press, 2005)

Genetic/Genomic Evidence for A Key Role of Polarized Endocytosis in Filamentous Differentiation of *S. cerevisiae*
Xiaofeng Wu and Yi Wei Jiang*. Yeast (In press, 2005)

Future Plan

The top priority for this research area is to obtain independent funding. I plan to resubmit the NIH R01GM070568 application with the following modified aims.

Aim 1. Screen for filamentation-specific *rad53* and *mec1* alleles to understand how Rad53 is activated in filamentous growth. (Modified old Aim 2)

Aim 2: Identify the genes that are required for *clb2*Δ-caused constitutive filamentous growth. (Modified old Aim 3)

Aim 3. Identify genes that are required for the activation of the filamentous MAPK pathway by Swe1 in nitrogen starvation-induced filamentous differentiation. (A new Aim)

Area 3: Peptide antibiotics

Human health is once again being threatened by bacterial infections due to increasingly widespread resistance to currently available antibiotics. To combat this threat, novel antibiotics are needed. We are searching for peptide antibiotics that are produced by soil bacteria. Peptide antibiotics have two potential advantages over the traditional antibiotics such as penicillin. First, tests indicate that it is more difficult for bacteria to develop resistance. Second, the structure of an antibacterial peptide can be easily manipulated to produce new antibiotic peptides of better therapeutic properties. We have isolated a new family of peptide antibiotics (TAMUS 2032 or BT) and identified the gene cluster encoding the nonribosomal peptide synthase. US and PCT patent applications have been filed to protect the intellectual properties on these peptides. TAMUS 2032 has shown impressive effects in preventing bacterial infections through immunomodulation and promoting growth in animal tests. The potential of this technology is enormous with a predicted peak royalty at $26-53 mil per year. Major drug companies are conducting evaluations for licensing.

Publications

Structure and Biosynthesis of the BT Peptide Antibiotic from *Brevibacillus texasporus* Xiaofeng Wu, Johnathan Ballard and Yi Wei Jiang*. Applied and Environmental Microbiology (In press, 2005)

The Efficacy of TAMUS 2032 (BT) in Preventing a Natural Outbreak of Colibacillosis in Broiler Chickens in Floor Pens.
Y. W. Jiang*, M. D. Sims, and D. P. Conway. Poultry Science (In press, 2005)

The Efficacy of TAMUS 2032 (BT) in Promoting Growth in Comparison to BMD in Broiler Chickens in Floor Pens
Y. W. Jiang*, Terry N. Terhune and D. P. Conway (submitted, 2005)

Patent

Compositions, Methods And Uses for A Novel Family of Peptides
Yi Wei Jiang, US (11/046,560) and PCT (PCT/US2005/003343) patent applications (01/2005)

Teaching Interests and Experience

I am willing and able to teach molecular biology and genetics at all levels. I have taught molecular biology and genetics to medical students for the past six years at COM/TAMUSHSC.

Lecture Topics

1. The structure of nucleic acids
2. DNA replication
3. Transcription
4. Translation
5. Regulation of gene expression
6. Mitosis
7. Meiosis
8. Molecular biology techniques in modern medicine
9. Molecular biology of cancer
10. Multi-factorial inheritance
11. Mitochondrial inheritance
12. Non-Mendelian inheritance
13. Population genetics
14. Developmental genetics
15. Gene therapy
16. Human DNA repair disorders

Medical Conference/Small Group Topics

1. Type I Diabetes
2. Type II Diabetes
3. Obesity
4. Atheroscolerosis
5. Hypertension
6. Alzheimer's Disease
7. Parkinson's Disease
8. Lysosomal Storage Disease
9. Arthritis
10. Osteoporosis
11. Breast Cancer
12. Leukemia
13. a1-Antitrypsin Deficiency
14. Cystic Fibrosis
15. Hemoglobinopathies
16. HIV and Acids
17. Asprin, the wonder drug
18. Telomerase, Cancer and Aging
19. Hypercholesterolemia