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Dr. Yves Brun
Systems Biology/Microbiology Faculty Search
Indiana University
Department of Biology, Jordan Hall 142
1001 E. 3rd Street
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Dear Dr. Brun,

I am writing to apply for the position of assistant professor (tenure-track) in the Department of Biology. I am currently a postdoctoral fellow in the laboratory of Dr. Leonard Guarente at the Massachusetts Institute of Technology. My research goal is to advance our understanding of aging and age-related diseases using genetics and functional genomics to elucidate the genes and cellular pathways that regulate aging.

My postdoctoral research has focused on the molecular pathways of aging in *C. elegans* regulated by the silent information regulatory (sir) gene, *sir-2.1*. Members of the Sir2 family encode protein deacetylases and have been shown to regulate lifespan in several model organisms. In one study, I focused on understanding the mechanism of *C. elegans* lifespan extension mediated by resveratrol, a naturally occurring compound found in red wine. Determining that resveratrol-mediated lifespan extension in *C. elegans* was dependent upon *sir-2.1*, I took a functional genomics approach to identify other candidate effector genes. Using microarray analysis I identified a family of prion-like genes involved in endoplasmic reticulum (ER) stress response that are both upregulated by resveratrol treatment and transcriptionally regulated by *sir-2.1*. Utilizing various molecular and genetic techniques I was able to demonstrate that altering expression of members of this family affects lifespan in a dosage-dependent manner. This is the first finding to directly implicate genes involved in ER function in lifespan regulation, and as such, represents a new avenue into aging research.

In addition to continuing my studies on the role ER stress genes in regulating lifespan, I also plan to investigate the function of the other *C. elegans* Sir2 homologs and their potential roles in cellular metabolism and aging. I also plan to expand my studies to include other dietary factors that may affect the aging process. The direction of my laboratory research will combine genetic and functional genomic approaches for gene discovery, with biochemical and molecular methods to define gene functions. The objective of this research will be to discover how genes that participate in specific cellular processes regulate aging and age-associated diseases such as neurodegenerative disorders, diabetes, and cancer.

I am eager to direct a stimulating research program and committed to teaching others, both in the classroom and the laboratory. In addition to my *curriculum vitae*, I have enclosed a summary of previous research, a statement of current and future research objectives, and a statement of teaching interests for your consideration. I have asked that my references forward their letters of recommendation to your attention. Please contact me if you need any additional materials in support of my application. I look forward to the opportunity to present my current work and future plans in detail.

Sincerely,

Mohan Viswanathan

Mohan Viswanathan, Ph.D.

Previous Research: Brandeis University, Dr. Susan T. Lovett (advisor)

The focus of my graduate research was on DNA exonucleases (Exo's) and the role they play in maintaining genomic stability in *Escherichia coli*. DNA exonucleases were once considered only to be minor players in secondary pathways of DNA recombination in *E. coli*. The results of my research, however, demonstrated that they actually play important roles in homologous recombination, DNA repair and mutation avoidance processes.

In our initial studies we demonstrated that three *E. coli* single-strand exonucleases (ssExo's); RecJ, ExoI, and ExoVII, shared overlapping roles in the repair of UV-induced DNA damage, likely facilitating the repair of damaged DNA and stalled replication forks through homologous recombination[1]. In addition, other genetic evidence from this study suggested the existence of other unknown ssExo's in *E. coli* involved in methyl-directed mismatch repair. This provided impetus for us to search for additional ssExo's in the *E. coli* genome.

The first ssExo that we found, exonuclease T (a.k.a. RNase T), was identified by a novel iterative selection high-copy suppressor screen[2]. Although ExoT was previously reported to be an RNase, we demonstrated that ExoT is actually a much more potent ssExo capable of substituting for the loss of other ssExo's *in vivo*[3]. The second Exo that we identified, exonuclease X, was discovered by virtue of its homology to ExoT. However, unlike ExoT, ExoX had potent exonucleolytic activity on both single-stranded and double-stranded DNA[4]. ExoX and RNase T are members of a superfamily of Exo's that share homology with DnaQ, the exonuclease subunit of DNA polymerase I. Unlike the other members of this superfamily, which are processive in nature, we found that RNase T and ExoX are distributive nucleases, removing only one or few nucleotides with each binding. This result demonstrated a notable dichotomy in function among members of this family of proteins.

Having identified ExoX, we were able to prove both genetically and biochemically that ExoI, ExoVII, RecJ and ExoX each play a role in the removal of misincorporated nucleotides during the process of mismatch repair[5]. We demonstrated that loss of these Exo's results in both increased mutagenesis due to loss of mismatch repair capacity and partial inviability caused by inability to repair mispairs[6]. Since components of *E. coli* mismatch repair are well conserved in higher organisms these findings also impact our understanding of eukaryotic mismatch repair.

In related work on the role of ssExo's in mutation avoidance, we reported the discovery of a mutation hotspot within a naturally occurring quasipalindromic (imperfect palindrome) sequence in the *E. coli* genome. To help understand the nature of this phenomenon we developed an assay system that allowed for molecular analysis of the mutations formed at the hotspot. From this analysis we were able to demonstrate that the mutations were created by mistemplated replication initiated within a hairpin-like structure formed by the quasipalindromic sequences. Furthermore, we demonstrated that ExoI, ExoVII, and the methyl-directed mismatch repair system of *E. coli* normally play a role preventing this class of mutations. This was the first study to identify genes involved in preventing quasipalindrome-templated mutations[7].

Over the course of my graduate training I gained expertise in bacterial genetics, molecular biology, protein purification, and protein biochemistry. In addition, I was responsible for training and supervising several graduate students, three of whom are co-authors on three separate publications. Guiding these students through the design and implementation of their experiments was a productive and rewarding experience that greatly influenced my decision to pursue an academic career in science.

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Molecular Pathways of Life Span Regulation in *C. elegans* Mohan Viswanathan, Ph.D.

Current Research: Massachusetts Institute of Technology, Dr. Leonard Guarente (mentor)

Over the past decade, studies in multiple model organisms have demonstrated that aging is a regulated process that can be manipulated genetically. Studies in yeast, flies, worms, and mice have led to the discovery of conserved genes, including members of the insulin/IGF-like pathway and the Sir2 gene family, that regulate life span. Furthermore, the identification of small molecules and the study of regimens that extend life span, such as calorie restriction, have also added to our knowledge about molecular aging pathways. Our understanding of aging and the onset of age-related diseases at the molecular level can be furthered by identifying global regulators of aging, the genes they control, and ultimately determining the biochemical processes that help maintain cellular function and individual fitness.

Role of ER-stress genes in regulating life span

The drug resveratrol, a naturally occurring compound found in grapes, has been linked to a number of health benefits associated with red wine consumption[1]. In a screen for small molecule effectors of Sir2 proteins, resveratrol was found to be an activator of human SIRT1 protein deacetylase activity[2]. To further our understanding of the role of Sir2 genes in regulating life span, we investigated the effects of resveratrol treatment on *C. elegans*[3]. We found that resveratrol extends *C. elegans* life span in a dosage-dependent manner that requires the *C. elegans* Sir2 homolog, *sir-2.1*. However, while life span extension by *sir-2.1* overexpression requires the insulin-like signaling pathway gene *daf-16* (see below), the same is not the case for resveratrol-mediated lifespan extension, suggesting a secondary pathway of *sir-2.1*-dependent life span regulation.

Microarray expression profiling revealed that resveratrol treatment induces expression of a number of genes belonging to the *pqn* gene family. *C. elegans pqn* genes encode prion-like glutamine(Q)/ asparagine(N)-rich domain-containing proteins[4]. A subset of *pqn* genes, some of which are activated by resveratrol, are designated as *abu* genes, for activated in blocked unfolded protein response. *abu* genes are upregulated in response to ER-stress caused by the accumulation of unfolded protein in the endoplasmic reticulum (ER)[5]. We focused our analysis on these genes to determine whether they play a role in *C. elegans* aging and resveratrol-mediated life span extension.

Knockdown of several *pqn* genes by RNAi shortens *C. elegans* life span, indicating a role for these genes in promoting longevity. RNAi of one gene in particular, *abu-11*, fully abolishes resveratrol-mediated life span extension, suggesting that *abu-11* is required for life span extension by resveratrol. Furthermore, we found that a number of the *pqn/abu* genes, including *abu-11*, are repressed by *sir-2.1*, indicating that in the case of *pqn* gene expression, resveratrol inhibits *sir-2.1* function. Several lines of transgenic worms created to overexpress *abu-11* demonstrated increased life span; supporting the contention, that *abu-11* is a regulator of aging.

Role of sir-2.1 in the insulin-like signaling pathway

• *sir-2.1* mutants

Overexpression of *sir-2.1* by high-copy transgene extends nematode life span up to 50% in a manner dependent upon the insulin/IGF-like signaling pathway gene, *daf-16*, which encodes a forkhead transcription factor[6]. Mutants that attenuate signaling in this pathway, such as *daf-2* (insulin-like receptor) mutants, lead to DAF-16 nuclear localization and the doubling of life span[7]. To help dissect the genetic pathway of *sir-2.1* function, I collaborated with the lab of Dr. Ronald Plasterk to screen libraries of mutagenized worms for *sir-2.1* mutants, obtaining a *sir-2.1* deletion mutant and an insertion mutant. Accordant with the fact that Sir2 genes are dosage-dependent regulator of aging in yeast and flies, loss of *sir-2.1* shortens *C. elegans* life span. The reduction in life span however is not epistatic to loss of *daf-16*, nor does it abolish *daf-2* mutant lifespan extension, suggesting that *sir-2.1* may act in other pathways to influence life span (see previous section). We are currently analyzing microarray data from *sir-2.1* mutants and low-copy overexpression worms to help identify potential downstream effectors.

• Analysis of SIR-2.1 expression

It has recently been determined that *sir-2.1* is in a two gene operon, driven by the upstream gene's promoter[8]. To confirm that sir-2.1 overexpression-mediated lifespan extension is a physiologically relevant phenomenon I constructed a *sir-2.1* expression construct under the natural operon promoter and produced transgenic lines using high-speed particle bombardment to produce low-copy number transgenic worms. These worms display extended life span, some as great as 50%, and show dependence on *daf-16*. Both SIR-2.1-GFP expression and immunolocalization of SIR-2.1 indicate nuclear expression, similar to yeast Sir2 and mammalian SIRT1 proteins[9]. Moreover, purified recombinant SIR-2.1 demonstrates NAD-dependent deacetylase activity. We are currently generating transgenic line expressing *sir-2.1* deacetylase mutants to determine whether life span extension due to

overexpression is indeed a function of deacetylase activity. Furthermore, I plan to examine tissue-specific overexpression of *sir-2.1* to determine if expression in specific tissues is sufficient for lifespan extension.

• Role of *sir-2.1* in calorie restriction

The regimen of calorie restriction (CR), where caloric intake is reduced by 30%, has been shown to extend life span in all organisms where it has been tested. In yeast and flies CR-mediated life span extension is dependent on Sir2[10; 11]. To assay CR in worms I developed a solid media that simultaneously enables control of food levels by preventing growth of an auxotrophic *E. coli* strain, and prevents worm loss due to burrowing (a phenomenon that occurs when media is depleted of food). This system of CR increases mean life span of wild-type worms by up to 50%. However, unlike yeast and flies, *sir-2.1* mutant worms still benefit from CR. In the future, I plan to determine if other *C. elegans* Sir2 paralogs are involved in CR-mediated lifespan extension.

Future Research:

C. elegans is a powerful tool in the study of aging; it is genetically tractable, amenable to functional genomic assays, and has a relatively short life span facilitating actual aging studies. *C. elegans* also shares a large number of conserved genes and metabolic pathways with higher organisms. Consequently, findings of biological significance in worms are often applicable to mammalian biology. Ultimately, I hope to steer the course of *C. elegans* research in my lab towards avenues that are pertinent to aging and age-related diseases in mice and humans.

Aim 1: ER-stress and aging.

The ER is responsible for the synthesis, folding, modification and delivery of proteins to sites within the secretory pathway and cell membrane. Diseases caused by mutations that alter the folding of secreted proteins include, diabetes and Alzheimer's, both of which are associated with aging. It is therefore possible that alterations in ER protein folding and trafficking play a role in aging and the onset of age-related diseases. In *C. elegans*, *sir-2.1* represses expression of members of the *pqn/abu* family of genes which are known to be activated by ER-stress and are thought to play a role in ER-stress response. To expand on our initial findings that expression of *pqn/abu* genes can alter worm life span, I plan to determine the manner in which *sir-2.1* regulates these genes as well as their physiological relevance to both ER stress and life span regulation.

• Role of *sir-2.1* in ER-stress regulation

To help define sir-2.1's role in regulating ER-stress response I plan to perform an epistatic analysis of *sir-2.1* mutants in combination with mutations in other ER unfolded protein response (UPR) pathway genes. Mutants will be analyzed for changes in development, survival, and response to ER-stress. Sir2 proteins do not have DNA binding domains and are often associated with other transcriptional regulators[12; 13; 14]. To isolate and identify proteins that specifically associate with SIR-2.1 following ER-stress induction, co-IP experiments will be performed using α-SIR-2.1 antibody and extracts from worms treated with the ER-stress inducer tunicamycin. Similarly, chromatin IP experiments will be performed to ascertain whether SIR-2.1 is present at the promoter of *pqn/abu* genes that we have previously found to be highly upregulated in *sir-2.1* mutants. To identify other factors involved in regulating the *sir-2.1* dependent ER-stress pathway, I plan to perform a genome-wide RNAi screen to find genes that when downregulated, activate GFP expression from the normally repressed *abu-11* promoter. These may include genes that promote *sir-2.1* expression or aid in its repressive function.

• Functional characterization of genes encoding glutamine-rich proteins

There are roughly one hundred *pqn* genes in *C. elegans*, and similarly large sets of Q/N rich proteins in other eukaryotic model organisms. Structurally Q/N-rich sequences are believed to be modular "polar zipper" protein-protein interaction domains that are prone to aggregation[15]. Glutamine rich domains are found in several amyloid proteins that cause neurodegenerative diseases and Q/N-rich domains are found in prion proteins, which remodel other proteins causing aggregation. Genome-wide two-hybrid[16] and microarray analysis[17] indicates that members of *pqn* family form large protein-protein interaction networks and are expressed in a co-regulated fashion. One possibility is that ER resident PQN/ABU proteins may act as surveillance system for misfolded proteins in the ER, perhaps keeping proteins in an unfolded state when environmental conditions favor improper folding or perhaps to target potentially harmful misfolded proteins for destruction. To understand the broader roles of these genes in ER function, I plan to focus on those *pqn/abu* genes regulated by *sir-2.1* that are required for normal life span. Worms overexpressing, or mutant, for these genes will be isolated and assayed for life span individually and in combination to determine if there is epistasis and/or synergy of life span effects. These strains will also be analyzed for changes in their ability to respond to ER-stress and for accumulation of protein aggregates.

The advent of *C. elegans* strains expressing polyglutamine-repeats fused to yellow fluorescent protein (YFP) has made *C. elegans* has a powerful tool in understanding the biology behind polyglutamine protein aggregation[18], a phenomenon associated with Huntington's disease and some neurodegenerative disorders. Long-lived insulin/IGF-like mutants have been shown to prevent age-dependent aggregation of polyQ-YFP proteins, as have heat shock chaperones and other protein folding genes[19; 20]. I plan to use these cytoplasmic polyQ-YFP strains along with ER-targeted polyQ-YFP (and polyQ/N-YFP) constructs to study the role of *sir* genes, *pqn/abu* genes, ER-stress, and calorie restriction in polyQ protein folding and aggregation. In addition to direct visualization of polyQ aggregation, we will also test for alterations in behavioral responses indicative of neuronal function. Touch response and chemotaxis normally demonstrate age-related decline in *C. elegans* and can be further attenuated by neuronal polyQ aggregation[21]. Changes in such behaviors will be a direct assessment of the effect of these genes on age-related neuronal function. If successful, this approach can be expanded to RNAi and mutagenic screens to find other genes that affect age-dependent polyQ aggregation and neuronal function through these pathways.

Aim 2: Role of *C. elegans* SIR2 paralogs in cellular metabolism and aging.

Apart from *sir-2.1*, *C. elegans* has three other Sir2 paralogs, *sir-2.2*, *sir-2.3*, and *sir-2.4*. I plan to determine the cellular function of these genes, and investigate if like *sir-2.1*, they play a role in regulating *C. elegans* life span. Taking a genetic approach, I will isolate and test null mutants and overexpression animals for effects on life span, and determine if they act in any of the known aging pathways. In addition, microarray analysis will be performed comparing wild-type, mutant and transgenic animals to help determine the identity of genes regulated by the various Sir2 worm paralogs. I have already obtained deletion mutants in *sir-2.3* and *sir-2.4* and generated low-copy transgenic lines for *sir-2.2* and *sir-2.3* as part of my collaborative work with Ronald Plasterk's lab.

To understand the cellular function of these proteins, I plan to clone full-length cDNAs for each of the genes and generate recombinant expression constructs for protein purification and subsequent antibody production. Immunolocalization and GFP fusion constructs will be made to determine tissue and subcellular localization, while purified recombinant proteins will be assayed for protein deacetylase and ADP-ribosylation activity. It is known that mammalian SIRT4, whose core domain most resembles *sir-2.2* and *sir-2.3*, is localized to the mitochondria, and SIRT6, which most closely resembles *sir-2.4*, is localized to the nucleolus[9]. Both mammalian proteins have been demonstrated to possess ADP-ribosylation activity[22; 23]. It will be of particular interest to determine if the *C. elegans* proteins have similar localization and functional profiles and even more interesting to determine if they have aging phenotypes. Since Sir2 genes share a great deal of homology in the core Sir2 catalytic domains, it will also be important to determine if any have overlapping role in cellular function. By combining mutants together in multiplex fashion, I hope to uncover any redundant or overlapping functions.

Loss of *C. elegans sir-2.2* function has recently been found to increase genomic instability in a genome-wide RNAi screen for mutator genes[24]. To investigate the role worm Sir2 genes play in genomic stability I plan to determine the mutation rate and mutation spectrum of various *sir-2* mutants (or by RNAi) in a forward mutator assay that detects a broad spectrum of mutations at the *unc-93* locus[25]. Further investigations into the mechanism of mutagenesis will be pursued contingent upon the types of mutational spectrums found.

Aim 3: Role of diet in *C. elegans* aging.

Diet plays a large role in the health and longevity of all organisms. Nutrient quality and availability naturally dictate quality of life and length of life span. As previously mentioned, the regimen of calorie restriction (CR) can significantly extend life span. While Sir2 homologs in flies and yeast both appear to be necessary for the life span extension benefits of CR, a similar result has yet to be found in *C. elegans*. I plan to test whether mutants in the other remaining sir genes either individually or in combination with each other and/or *sir-2.1* prevent CR-mediated life span extension. Furthermore, I plan to perform time course microarray analysis of aging worms fed either *ad libitum* or under CR conditions to aid in uncovering genes that may play a role in CR-mediated life span extension.

Under laboratory conditions *C. elegans*' diet consists solely of *E. coli*, which in itself can affect nematode life span. For example, *E. coli* mutants that fail to make the redox-active lipid coenzyme Q, utilized by worms in their mitochondrial electron transport chain, significantly extend worm life span[26]. Q-less diet is believed to extend lifespan by reducing levels of damage-causing reactive oxygen species generated in the mitochondria. In addition, as worms age and their bodies degenerate, their food source can actually become pathogenic. Using an *E. coli* transposon insertion library, I plan to screen for *E. coli* mutants that alter development or adult life span of wild-type worms. Such genes may uncover specific dietary factors and bacterial genes that trigger antimicrobial defenses that affect nematode lifespan. Similarly, I plan to also perform genome-wide RNAi screens to find *C. elegans* genes that lead to the proliferation of fluorescent-protein-expressing *E. coli* within the worm and test these candidate genes for life span effects. Such genes may play a role in innate host defense and could be conserved antimicrobial factors.

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Statement of Teaching Philosophy and Interests:

As a mentor and teacher, I aim to achieve three fundamental goals. The first goal is to impart to students, a working knowledge of facts and concepts that will aid them in understanding varied topics and addressing experimental questions in diverse fields. The second goal is to help students develop critical thinking skills that allow them to assess the strengths and weaknesses of arguments and to develop research methods to answer questions in undeveloped fields. The third goal is for students to develop oral and written communication skills, and to work collaboratively with their peers. While all three goals are important to the biological sciences, they are useful in other aspects of life and can be applied in any career path.

In undergraduate courses, such as cellular biology and molecular biology, students are expected to learn a substantial amount of fact-based material. My approach to teaching these types of classes is to have students rely on the contextual understanding of facts rather than on memory alone. This is achieved by describing the initial experimental process that led to the discovery of specific biological facts and by relating difficult concepts to simpler ones using analogies. In addition, by encouraging classroom interaction between students and promoting inquiry-based approaches to new concepts students are drawn into active learning, thereby fostering a deeper understanding of material and critical thinking skills.

In upper level undergraduate and graduate level classes I prefer the incorporation of experimental literature based instruction into the standard lecture format. In undergraduate level courses, this would include assignments to write concise abstracts based on experimental data, or to have groups of students collaborate to write various sections of a paper to be critiqued by peers in class. At the graduate level, students would be asked to read and lead discussions of historically based papers that represent a particular field of study. In these types of courses, open book exams with experimentally driven problems would emphasize critical thinking and the understanding of fundamental concepts rather than memorization of facts. In my experience, this type of interactive-style of learning provides students with much-needed opportunities to experience a collegial environment while engaging in collaborative work. Furthermore, it is an ideal setting in which to hone critical thinking and oral presentation skills.

As an assistant professor, I plan to utilize my past teaching experiences and the approach I have described above to structure my classroom curriculum and mentor students in my own lab. As a graduate student, I have had formal training and experience in teaching cellular biology, molecular biology and genetics. With my experience and knowledge of aging biology, DNA repair, DNA recombination and model organism genetics I am well suited to teach advanced-level undergraduate and graduate classes in these areas. In addition, I would also be comfortable teaching a broader range of biology-related subjects.