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

Dear Dr. Brun,

This is a very strong letter of recommendation for **Mohan Viswanathan**, who has been a postdoctoral fellow in my lab for four years. Mo is a bright, determined, and productive young scientist who is certain to enjoy a successful career as an independent investigator at a top academic department. He is among the top five postdocs I have had out of about 40 over 24 years at MIT. He came to my attention as a graduate student at Brandeis, when he was recommended to me by Jim Haber (Mo was actually Sue Lovett's student). He had a stellar graduate career with six first author papers in good journals and secured a JCC fellowship.

When Mo came to my lab, I asked him to learn *C. elegans*, even though we were new in that business ourselves. He has done so, and has become a real expert in the process. As an example of this expertise, I will first describe how he has contributed mightily in generating reagents used in his Dev. Cell paper, and another paper on which he is second author. He generated an excellent antiserum to SIR-2.1 protein and used it in assays for quantitating SIR-2.1 protein levels in worm strains expressing various levels of the protein. He has constructed strains with deletion mutations in *sir-2.1* and *sir-2.2* genes by EMS mutagenesis, PCR screening, and backcrossing to N2. He has built strains with low copy over-expression of SIR-2.1 by the bombardment method. He has also generated transcriptional array data, with Stuart Kim, for strains with the *sir-2.1* deletion or SIR-2.1 over-expression.

His studies have implicated a novel pathway of ER-stress maintenance in longevity in *C. elegans*. This study began by testing the effect of the putative Sir2 activator, resveratrol, on worm lifespan. Mo found that the compound indeed extends lifespan, and depends on *sir-2.1* to do so. But, surprisingly, the compound appeared not to depend on *daf-16*, the forkhead gene required for life extension by over-expressing SIR-

2.1. This finding suggested that resveratrol affected a novel pathway of genes that were sir-2.1 dependent and influenced lifespan.

Mo used transcriptional profiling to identify sets of genes regulated by resveratrol. Interestingly, he discovered a set of genes termed pqn or abu that had been implicated in ER stress. Mo went on to show that these genes were responsible for the effect of resveratrol on lifespan functionally. Interestingly, these genes are also regulated by sir-2.1. However, since resveratrol had been billed as a Sir2 activator, we expected these genes would be activated by sir-2.1. Instead, they are repressed by sir-2.1. This suggests that resveratrol can inhibit sir-2.1 in its ability to repress the pqn/abu genes. The compound does not affect the ability of sir-2.1 to function in its canonical way in the daf-16 pathway. So the conclusions are several fold. First, up-regulation of a novel set of ER stress genes can extend lifespan in worms. Second, these genes are normally repressed by sir-2.1. Thus, the increase in lifespan by over-expressing SIR-2.1 is NOT due to these genes (but to effects on DAF-16). And third, resveratrol can affect Sir2 in both directions, activation, as was described before, or repression, as revealed here. This work will appear with Mo as first author in Dev. Cell.

Also, Mo has made a significant contribution to the project of a graduate student, Ala Berdishevsky, to study how SIR-2.1 modulates the daf pathway. In brief, the conclusion of this study is that SIR-2.1 binds to 14-3-3 proteins, and the latter proteins facilitate the binding of SIR-2.1 to DAF-16 after stress treatments. Thus, SIR-2.1 does not work within the insulin signaling pathway to extend lifespan, but in parallel, stress sensitive pathway that converges on DAF-16. Mo will be second author on a paper that is in review at a major journal.

Finally, Mo has a significant body of data on sir-2.1 and other sir2 genes that will constitute another paper. I think he is ready and extremely able to assume an independent position and run his own lab. As is my policy, I will let Mo take his project and will not continue working directly in the area he is investigating.

In summary, Mohan Viswanathan is a very talented young scientist and is a very strong candidate for a faculty position in your department. He has my highest recommendation, and I strongly suggest that you invite him for an interview. He is very well trained in molecular biology in general and the details of *C. elegans* biology in particular. He will be a very successful lab head and a great colleague to have around.

Sincerely



Leonard Guarente

Novartis Professor

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