UNIVERSITY OF CALIFORNIA, DAVIS

BERKELEY ▯ DAVIS ▯ IRVINE ▯ LOS ANGELES ▯ MERCED ▯ RIVERSIDE ▯ SAN DIEGO ▯ SAN FRANCISCO SANTA BARBARA ▯ SANTA CRUZ

Michael A. Savageau, Ph.D.
Distinguished Professor and Chair
COLLEGE OF ENGINEERING
DEPARTMENT OF BIOMEDICAL ENGINEERING
masavageau@ucdavis.edu

2311 Genome & Biomedical Sciences Facility
451 EAST HEALTH SCIENCES DRIVE
DAVIS, CALIFORNIA 95616-5294
(530) 754-8375 (Phone)
(530) 754-5739 (Fax)

November 3, 2005

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

Re: Letter of Reference
for Dr. Rui Alves

Dear Dr. Brun,

I am very pleased to write this letter of recommendation on behalf of Dr. Rui Alves. I have had a number of bright graduate students and postdoctoral fellows over the years, but Rui stands out as among the very best. Even as a graduate student he had acquired command of a vast number of bioinformatics tools, well beyond those typically used in my own group, and then he fearlessly launched into the development of his own approaches when confronted with a demanding problem. He is creative, full of initiative, and helpful to others. Given these characteristics it is not surprising that he was also one of the most productive students I have known.

Some background regarding Rui's PhD training may be helpful. Because Portugal has not had a strong scientific tradition, it has few world-class investigators to train the next generation of investigators. To deal with this problem, they have devised an innovative training program. They select a small number of their very best students, run them through two years of demanding courses taught by professors invited from around the world who are leaders in the various fields, and then fully fund the students to due their research anywhere in the world with prominent investigators of their choosing. These students are incredibly independent, and they receive top-notch training. Rui is a product of this training program.

I was fortunate to have Rui work as a graduate student in my group at Michigan for four and a half years. After exploring several potential topics for his thesis work, he focused his effort on numerical methods for rigorously comparing the function of related biochemical systems that exhibit alternative designs. The goal was to determine the selective advantages of each design. Although a symbolic (as opposed to numerical) method was previously developed for this purpose, it has limitations. In some cases, this method reveals clear qualitative differences, but the magnitude of these differences might actually be insignificant. In other cases, this method gives ambiguous answers, with one design superior for some parameter values and the alternative design superior for other values, and yet one design might be far superior on a statistical basis when a large sample of realistic parameter values is examined.

Rui developed a numerical method for making well-controlled comparisons that largely circumvents the limitations of the earlier method. By constraining the alternatives to be rigorously equivalent in other aspects, unrelated to the difference in design under consideration, and by randomly sampling potential values for the parameters that define the alternative designs, he was able to uncover functional differences between the alternatives that are general in a statistical sense. This method also gives a quantitative estimate of the differences. This has been a very significant methodological advance in the field. Rui has used this numerical method to examine a number of variations in design for metabolic pathways and signal transduction cascades. I will not go into the specific details of his results, but simply note that this work has led to several papers, six of which had already been published in peer-reviewed scientific journals by the time he left my group.

Rui went on to postdoctoral work first with Michael Sternberg in England where he developed his interest in structural bioinformatics. He subsequently went to work with Albert Sorribas in Spain where he developed an approach to pathway elucidation that integrates structural genomics and kinetic modeling. This led to a new hypothesis regarding the pathways for iron-sulfur cluster synthesis in yeast. Although I am less familiar with the work in this postdoctoral period, I do know that Rui independently initiated these projects, as he did with his PhD project. It also is clear that Rui has continued to publish at a similar rate in first-rate journals.

Rui is currently an Assistant Project Scientist in the Department of Biomedical Engineering at UC Davis. In this position he has initiated another independent research project involving the cognate amino acid bias in the composition of amino acid biosynthetic enzymes. Using comparative genomic approaches with bacteria he has discovered a statistically significant selection for low cognate bias and a profile of bias that appears to be a “fingerprint” reflecting the evolutionary history and ecological niche of the organism. This discovered has broad implications and he is about to submit an NSF grant proposal to expand the work. In Davis, Rui also is working with Professor Mitchell Singer in Microbiology, who is attempting to identify physiologically meaningful interactions among sensor and response-regulator proteins from a large number of possibilities in myxobacteria. Rui has taken sequence data for many of the proteins, developed 3-D models of their folded structures, and performed simulated docking experiments to score the potential interactions. The result is a ranked list of protein pairs that has been helpful in prioritizing the experimental effort in the Singer lab.

Rui has had some teaching experience, both by invitation back in Portugal and as an occasional replacement for me when I am out of town. He has excellent command of his material, but he still needs more experience in finding the right level of presentation for his audience. At times he hits it just right; but at others, he places too much emphasis on material that his audience can readily grasp and too little on material they might find more difficult. He is a quick learner, and I have no doubt that he will remedy this with more teaching experience.

Rui has a great sense of humor, and he gets along with everyone in the laboratory and the department. He is stable, reliable and scrupulously honest. Rui is laid-back and unassuming, so there is much more to him than first appearances might suggest. He is a true scholar with a sincere interest in both research and teaching. He has a highly developed sense of scientific curiosity. His questions are always for the purpose of advancing the discussion and not simply demonstrating his

command of a subject. He has a quiet confidence in his own ability. He is persistent, reads the literature and thinks for himself. He will build on his strengths and exploit new opportunities available to him. He is both imaginative and hard working, which are strong indicators of future success. I should not fail to mention one of Rui's highly desirable characteristics that would be particularly valuable for a new program with many building tasks (as I have seen first hand in my job here!), Rui anticipates needs and generously volunteers his time and effort.

Rui is now ready for a regular faculty position. However, he finds there are no opportunities for him in Portugal. This is due to a flaw in the Portuguese training system described above. Portugal is in the midst of a cyclic downturn in its always-fragile economy, and this translates into a lack of positions available when its scientists attempt to return. After a thoughtful analysis of his options, Rui has decided to begin applying for full-time academic positions in the US. He would be well qualified for a regular faculty position emphasizing genomic approaches to cell and molecular systems.

In summary, I give Rui my strongest endorsement. He already has produced an important body of work with a clear and distinctive scholarly theme. His work is highly original and represents a significant contribution to the field. On a personal level, he has been a stimulating, resourceful and delightful colleague. Rui will be a credit to any program with which he is associated.

If I can be of any further assistance, please do not hesitate to call on me.

Sincerely yours,

Michael A. Savageau

MAS/mmo