UNC
SCHOOL OF MEDICINE
DEPARTMENT OF
PHARMACOLOGY

Timothy C. Elston, Ph.D.

University of North Carolina at Chapel Hill
Department of Pharmacology
Mary Ellen Jones, CB 7365
Chapel Hill, NC 27599
Phone: (919) 962-8655
Email: telston@amath.unc.edu

October 25, 2005

Letter of Recommendation for **Necmettin Yildirim**

Dear Search Committee,

I am pleased to write a letter of recommendation for Necmettin Yildirim. Necmettin has been a postdoctoral fellow in my research group for the past two years. While at the University of North Carolina (UNC), Necmettin has been involved in an interdisciplinary project focused on understanding signal transduction in the yeast pheromone response pathway. This project is being carried out in collaboration with Dr. Henrik Dohlman's laboratory (Biochemistry, UNC). Dr. Dohlman is a world expert on the pheromone response pathway. The mating response system in yeast is arguably the best-characterized signaling pathway of any eukaryote, and has served as a prototype for hormone, neurotransmitter, and sensory response systems in humans. The initial phase of the project focused on pathway deactivation by a regulator of G-protein signaling (RGS) protein. Necmettin developed a mathematical model that described the time-dependent behavior of the receptor, G-protein, and RGS protein. The model was compared with time-series and dose-response data from Dr. Dohlman's lab. This analysis revealed several features of the data that were inconsistent with the model's predictions. To account for the differences between model output and experimental data, it was necessary to postulate that the RGS protein was degraded in a pheromone-dependent manner. This motivated new experiments that reveled that RGS is ubiquitinated and degraded in response to pheromone stimulation. The results of these investigations were published in the *Journal of Biological Chemistry* and featured in *Science's STKE.*

Next Necmettin extended the model to include a more detailed description of the biochemical steps that regulate receptor and G-protein activation. The revised model was shown to be consistent with data from fluorescence resonance energy transfer experiments performed by Yi et al. (PNAS, *100*, 10764-10769, 2003) that measured the early time response of the pathway. The model also suggested protein degradation as a contributing factor to pathway deactivation. These results were recently published in *Methods in Enzymology.*

Recently, Necmettin has been developing computational models of the mitogen activated protein kinase (MAPK) portion of the pathway. The models are being used to investigate possible mechanisms of pathway specificity. Distinct cellular signaling pathways often use common signaling proteins, and establishing the mechanisms that enable cells to maintain signal specificity is a fundamental question in cell biology. The mating and invasive signaling pathways of yeast are a typical example. These two pathways involve distinct receptors and MAP kinases; however, both pathways use a common set of intermediary kinases. Time course data from the Dohlman lab are being used to discriminate between 5 different hypothetical models. Necmettin has shown that a model in which the MAPK Fus3 directly activates the phosphatase Ptb2, which in turn deactivates the MAPK Kss1, is required to account for all the experimental data. These investigations suggest a novel mechanism for pathway specificity involving MAPK regulation. Experiments designed to confirm the model's predictions are underway. A novel feature of this research is the use of Markov Chain Monte Carlo techniques to explore the robustness of the model to changes in parameter values. A manuscript of these results is in preparation.

While at UNC, Necmettin has taught two classes Math 31 Calculus of Functions of One Variable and MATH 147 Linear Algebra for Applications. As his postdoctoral mentor, it is my duty to observe Necmettin's teaching. Necmettin genuinely enjoys teaching and it shows. Necmettin is always well prepared for class. His lectures are clearly thought out, and he encourages student participation. He is a very enthusiastic instructor who uses practical examples to motivate mathematical methods. His office hours are well attended, and he is liked by the students. Next semester, Necmettin will teach a section of Math 31 designed for biology students. This course is still in a developmental stage, and I expect Necmettin's input to significantly improve the class.

Necmettin is a very hard worker with a real interest in biology and interdisciplinary research. He interacts very well with the members of Dr. Dohlman's lab, and he has provided valuable guidance for several of my graduate students. Necmettin is a very friendly individual who is well-liked by all the applied math postdoctoral fellows and graduates students. He possesses the motivation and work ethic required to succeed in academics. I expect him to do very well in his next position.

Sincerely,

Timothy C. Elston, Ph. D.
Associate Professor of Pharmacology

Mary Ellen Jones Building, CB#7365, Chapel Hill, North Carolina 27599-7365
Phone (919) 966- • Fax (919) 966-5640 • @med.unc.edu